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American Journal of Obstetrics and Gynecology

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Original Communications

THE SIGNIFICANCE OF ENDOCRINE ASSAYS IN THREATENED AND HABITUAL ABORTION*

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THE problem of the mechanism of abortion, both threatened and habitual, has been much discussed. Numerous claims for good therapeutic results from the treatment of these conditions with gonadotrophic extracts of pregnancy urine, progesterone and vitamin E, have been made. On the other hand, it has been clearly recognized by Huntingdon,^{1, 2} Rock,³ and others that in a majority of cases of abortion the gestation is abnormal or the fetus already dead when the symptoms appear. The evaluation of the results of therapy with progesterone has been made very difficult, owing to the above-mentioned fact and also because it is not easy to determine how many cases of threatened abortion, in which the fetus is not dead at the time of onset of symptoms, will carry through with ordinary routine methods of therapy. It was thought that further light might be shed on this subject by a detailed study of some of the endocrine factors which are of importance in the physiology of normal pregnancy.

The present investigation therefore deals with a study of the excretion of prolan (gonadotrophic substance), estrogens, and sodium pregnandiol glucuronidate in the urine of 35 cases of threatened or habitual abortion. Twenty-one of the patients were under the direct care of one of us (J. S. H.). The rest were referred for assay by other

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their "Original Communications."

gynecologists. In the interest of conserving space we here report only 25 of these cases. It may be well first to review the curves of excretion of these substances in normal pregnancy and to discuss the interpretations which may be drawn from them as to the physiologic changes taking place.

Prolan appears in the urine almost immediately on implantation. Kurzrok and others⁴ and Browne and Venning⁵ showed that it could be detected ten to thirteen days after the appearance of the gonadotrophic substance which occurs just before ovulation. In another case we have found that it appeared eleven days after ovulation as approximated from the time of onset of pregnandiol excretion. The rate of excretion rises rapidly after this to reach a maximum about fifty to sixty days after the beginning of the last actually occurring menstrual period, in most cases.⁵⁻⁸ The height of this peak varies considerably in different cases and may be as high as the concentrations formerly thought to be characteristic of chorio-epithelioma.⁹ The maximum excretion is maintained usually for only a few days and is followed by a rapid fall. A low level is reached at about one hundred to one hundred and twenty days. Thereafter the level of excretion in most cases remains relatively constant until parturition, after which it declines to zero in five to ten days. In a few cases a secondary rise of prolan excretion occurs in the sixth to the eighth month and lasts for a varying period of time.^{10, 11} Estrogens were found by Smith and Smith⁷ and Mason and Gustavson¹² to follow the usual excretion curve of the menstrual cycle through the period of conception. The drop in excretion which was expected premenstrually was only slight, and the excretion rate rose again after the time of the missed period. Both Browne and Venning,⁵ and Smith and Smith⁷ found variations in some cases in the excretion of estrin in the first few months of pregnancy which they interpreted as having a cyclic character. It had been shown by Zondek that the rate of estrin excretion rises rapidly between the third and fourth months of pregnancy. It reaches a maximum in the eighth or ninth month, and disappears within a few days after labor. Browne, Henry, and Venning¹¹ found this maximum to vary between 15,000 γ and 40,000 γ per twenty-four hours in the cases which they studied.

Sodium pregnandiol glucuronide is an excretion product of corpus luteum hormone and with certain limitations is believed to reflect the amount of progesterone being formed in the corpus luteum or elsewhere. This compound is absent from the urine during the follicular phase and first appears about twenty-four to thirty-six hours after ovulation. In most normal individuals the excretion lasts for ten to twelve days and the total amount excreted is between 45 and 55 mg. expressed as pregnandiol. Ordinarily the excretion stops one to three days before the onset of bleeding, but in a few cases the excretion continues up to the time of bleeding (Venning and Browne,¹³ Wilson and others,¹⁴ Hamblen and others,¹⁵ Stover and Pratt¹⁶). Two cases have recently been studied by us through the period of conception. In one case in which the rate of excretion was low there was a sudden increase eleven days after the day on which ovulation was believed to have occurred; in the other case there was no appreciable change over the time of implantation. In early pregnancy the level of excretion is the same as the maximum reached during the normal menstrual cycle, that is from 5 to 10 mg. per twenty-four hours. In this connection it may be pointed out that Browne and Venning¹⁷ showed that subcutaneous

injections of gonadotrophic substance from pregnancy urine (physex) given daily or every other day during the luteal phase of the menstrual cycle would prolong the corpus luteum phase, increase the output of pregnandiol, and delay menstruation. They found that the response of different corpora lutea to the same amount of injected gonadotrophic substance varied greatly. Further, that after a varying time, continuing the dose of physex at the same level failed to maintain the corpus luteum, pregnandiol excretion decreased and finally ceased and menstruation began in spite of continued injections. This led them to suggest that the corpus luteum might require increasingly large amounts of prolan to maintain its function as it grew older, and to speculate whether the rapidly increasing amounts of prolan formed in early pregnancy could be given teleologic significance on this basis. The time at which the excretion of pregnandiol begins to rise from this level varies considerably in presumably normal cases, but it is most often between the seventieth and ninetieth days after the beginning of the last menstrual period. The amount excreted rises usually parallel to the rise of total estrogens and reaches a maximum in the ninth month. The maximum is very variable, usually between 60 and 105 mg. per twenty-four hours, in some cases somewhat lower, and the compound disappears abruptly within twenty-four hours of delivery, but here the presence of blood may interfere with the detection of small amounts. In one case in which catheter specimens were obtained, 7 mg. were detected per twenty-four hours in the first three days after labor. Before labor in this case the value had been the usual one for late pregnancy.

Figs. 1, 2, and 3 show the values for prolan, pregnandiol and total estrogens, with rough average curves in eight cases of normal pregnancy. Not all of these cases were assayed throughout the whole period of gestation. Table I gives the variations in the values obtained throughout pregnancy. This table is derived from the same eight cases.

TABLE I. VARIATIONS IN URINARY EXCRETION OF PREGNANDIOL, ESTROGENS AND PROLAN IN EIGHT CASES OF NORMAL PREGNANCY

DAYS	PREGNANDIOL MG./24 HR.	TOTAL ESTROGENS GAMMA/24 HR.	PROLAN R. U./24 HR.
28- 56	5- 11	200- 1,000	700- 50,000
56- 84	6- 20	250- 2,400	10,000-200,000
84-112	10- 28	800- 4,000	3,000- 28,000
112-140	13- 35	1,000- 7,000	2,000- 10,000
140-168	22- 52	3,000-14,500	1,000- 10,000
168-196	40- 72	7,500-18,000	1,000- 15,000
196-224	48- 85	7,500-23,000	3,000- 13,000
224-252	55- 95	10,000-25,000	1,000- 24,000
252-280	60-105	15,000-40,000	2,000- 10,000

Days are counted from the first day of the last actually occurring menstrual period.

It has been known for a long time that both ovaries or the ovary containing the corpus luteum could be removed and pregnancy continue to term. The time at which the ovaries have been removed varies.

Studies of estrogen excretion were made by numerous investigators, and it was found by Waldstein¹⁸ and von Probstner¹⁹ that, while the excretion might be low immediately after operation, in the later months of pregnancy it reached normal values. A good review of the subject is given by Guldberg²⁰ who concludes that the placenta is the site of production of estrogens during pregnancy. It had previ-

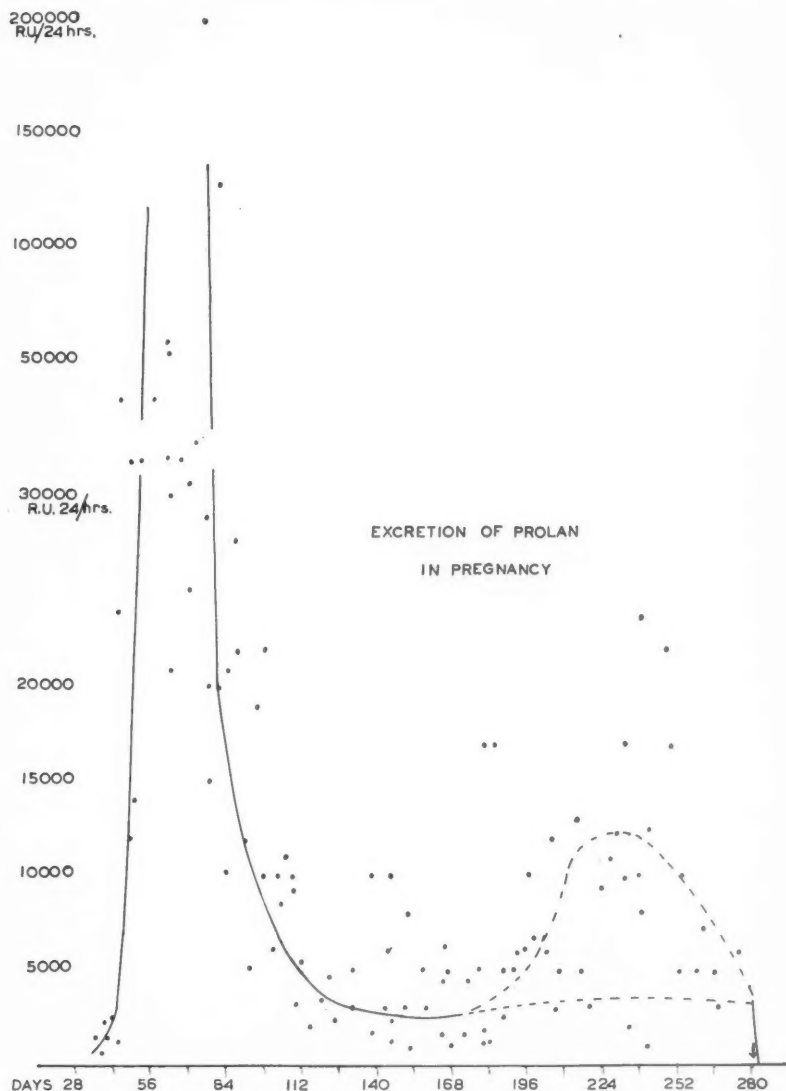


Fig. 1.—Excretion of prolactin in the urine of 8 patients with normal pregnancy. The dotted part of the curve represents the two types of excretion seen in late pregnancy, with and without a secondary rise in rate of excretion.

ously been generally assumed that corpus luteum hormone was unnecessary in the later months of pregnancy, because it had been found that the corpus luteum usually degenerated about the third month. Ehrhardt²¹ and Adler, de Fremery and Tausk²² found small amounts of progesterone activity in the placenta at term and Guldberg²⁰ showed that progesterone activity was present in the full-term placenta of

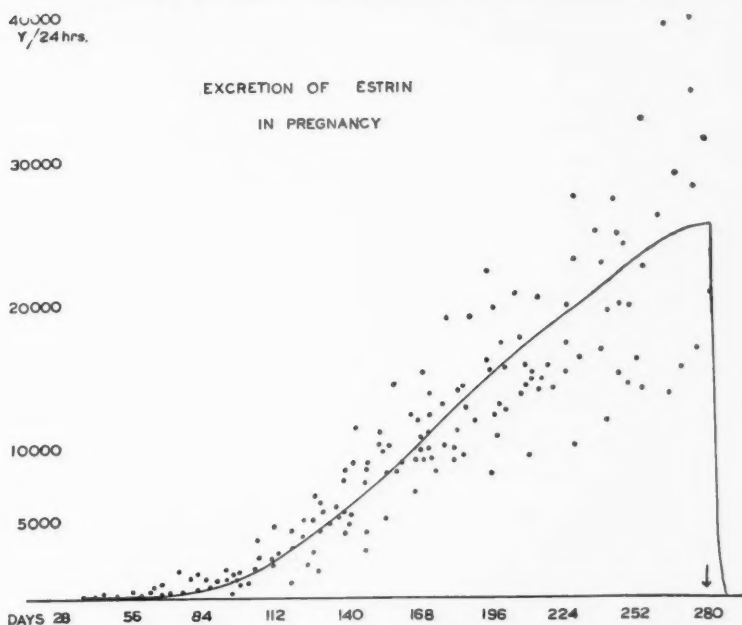


Fig. 2.—Excretion of total estrogens in the urine of 8 patients with normal pregnancy. The values are expressed in gamma excreted per twenty-four hours. Those under about 500 gamma are determined by biologic assay, those above this figure by a colorimetric method.

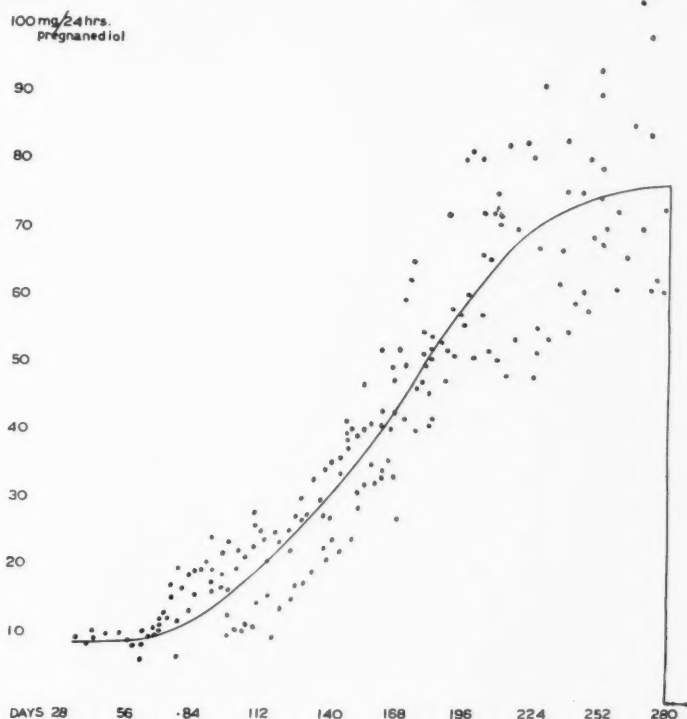


Fig. 3.—Excretion of pregnandiol in the urine of 8 patients with normal pregnancy.

a patient from whom both ovaries had been removed on the one hundred and thirty-third day. These findings suggested that the placenta might form corpus luteum hormone. In a case in which the ovary containing the corpus luteum was removed on the one hundred and fourth day, it was reported by Browne and others²³ that pregnandiol continued to be excreted up to term; the rate of excretion was within normal limits. Jones and Weil²⁴ confirmed this in a study of one other patient in whom the ovary was removed at the fifty-fourth day.

It was not until studies on pregnandiol were made that it was appreciated that large quantities of progesterone were being formed in late pregnancy and that it was rendered probable that most of this was being formed by the placenta.

The details of the normal values for the excretion of prolan, estrogens, and pregnandiol upon which Figs. 1, 2, and 3 and Table I are based will be published elsewhere. Consideration of the curve of excretion of prolan led Browne and Venning⁶ to suggest a theory concerning the physiologic relations of ovary and placenta during pregnancy and with regard to the transfer of site of formation of estrogens and progesterone from ovary to placenta at about the third month. Subsequent studies on the pregnandiol excretion during the normal menstrual cycle and pregnancy, the effect of pregnancy urine gonadotrophic substance on the corpus luteum mentioned above and the effects of ovariectomy on pregnandiol excretion during pregnancy have led to a better understanding of the endocrine relations during conception and pregnancy, particularly with regard to progesterone, and to a further elaboration of the theory which is presented here.

The normal corpus luteum ordinarily begins to function between twenty-four and thirty-six hours after ovulation and continues to function for ten to twelve days. Embryologists agree that the ovum takes approximately ten days to migrate down the tube and to become implanted in the endometrium. From the time at which prolan appears in the urine during the period of conception, it is probable that the chorion begins to secrete this substance almost immediately on implantation. The prolan usually maintains the corpus luteum function at the same level as the maximum attained during the menstrual cycle, but sometimes at a slightly higher level. It will be seen from this that the time relations during conception are rather exact. If for example the corpus luteum secretes progesterone for only seven days instead of ten or twelve, then by the time the ovum is ready to implant the corpus luteum will have ceased to function and implantation will not take place, since degeneration of the endometrium or even menstruation has begun. Such a short corpus luteum phase has been observed in some patients with sterility in whom no other cause for infertility has been detected. The rapid rise in production of prolan in early pregnancy may be necessary for increased stimulation of the corpus luteum to maintain it as it grows older.

In normal pregnancy, pregnandiol excretion may begin to rise from the level obtained after implantation as early as the seventieth day or perhaps a little earlier, but in other cases the rise fails to occur

until the hundredth day without any abnormal symptoms manifesting themselves. This rise is interpreted as due to the beginning of secretion of progesterone by the placenta. A few cases in which the ovaries have been removed earlier than the seventieth day and pregnancy has continued, make it probable that in some cases the placenta may begin to secrete earlier than this time. The rate of secretion of progesterone by the placenta gradually increases after this time up to term. The amount secreted varies in different individuals and in the same individual in consecutive pregnancies. It may depend upon the mass of placental tissue. There seems to be no significant change in progesterone metabolism immediately before labor, but progesterone ceases to be formed when the placenta separates, and its excretion product disappears from the urine shortly after this. The chorion is the source of prolactin from conception to term. In the first part of pregnancy estrogens and progesterone are formed in the ovary. At a varying time, but usually from the seventieth to ninetieth day, the placenta begins to secrete these substances. In most cases the corpus luteum ceases to function shortly after this. The placenta continues to form these substances in gradually increasing amounts until term. There is a transfer of function from one site of formation of progesterone and estrogens to another occurring usually in the third month. The cases presented below will illustrate the significance of this conception for the mechanism of the causation of abortion.

METHODS

Twenty-four-hour specimens of urine were collected, a few drops of tricresol were placed in the containers as preservative. In connection with the collection of twenty-four-hour specimens, it is naturally very important to be sure of the completeness of collection. In collecting specimens of urine over prolonged periods of time from the same patients, it has generally been found that remarkably even results are obtained in the day-to-day excretion of pregnandiol. It is only fair to state, however, that some of the fluctuations seen in the figures may be due to faulty collection, particularly when as in the case of occasional specimens the patients had not been trained in the collection of the urine. It is important to keep the specimens cool and to do the determinations as soon as possible after collection, in view particularly of the tendency of pregnandiol glucuronide to be hydrolyzed to free pregnandiol. Care was taken as far as possible to prevent blood from contaminating the urine. Prolactin was assayed and extracted by the same method as that used by Browne and Venning,⁶ the units are also the same and are expressed as rat units per twenty-four hours. Estrogens were extracted with ether after hydrolysis with zinc and hydrochloric acid (Smith and Smith) and assayed either on the immature twenty-one-day-old hooded rat or determined by the method of Venning and others,²⁶ depending upon the amount present. If the value was below 500 γ per liter, it was repeated on the rat assay. The values below about 500 γ in the tables and figures are therefore in rat units, those above are in gamma of total estrogens. The changes from one type of estrogen to another found to occur in pregnancy by Smith and Smith²⁵ will not affect the results obtained by the chemical method, since the amount of color developed from estrone, estriol and estradiol are approximately the same. Pregnandiol was determined by the method of Venning.^{27, 28} It should be emphasized that the values in this and other papers by the authors are expressed as milligrams of pregnandiol per twenty-four hours, not as milligrams of sodium pregnandiol glucuronide.

In all cases the time of pregnancy is reckoned from the first day of the last actually occurring menstrual period. In connection with the determination of

pregnandiol in the presence of blood, it may be stated that when the amount of pregnandiol present is below 4 or 5 mg., the presence of blood in the specimen tends to obscure the final identification of the complex. In the figures, Curve 1 represents prolant excretion, Curve 2 pregnandiol excretion, and Curve 3 that of total estrogens.

REPORT OF CASES

The cases will be divided into three groups. The first group comprises those patients in whom abortion actually occurred, the second those showing symptoms of threatened abortion, but in whom the gestation continued (these cases may or may not have had miscar-

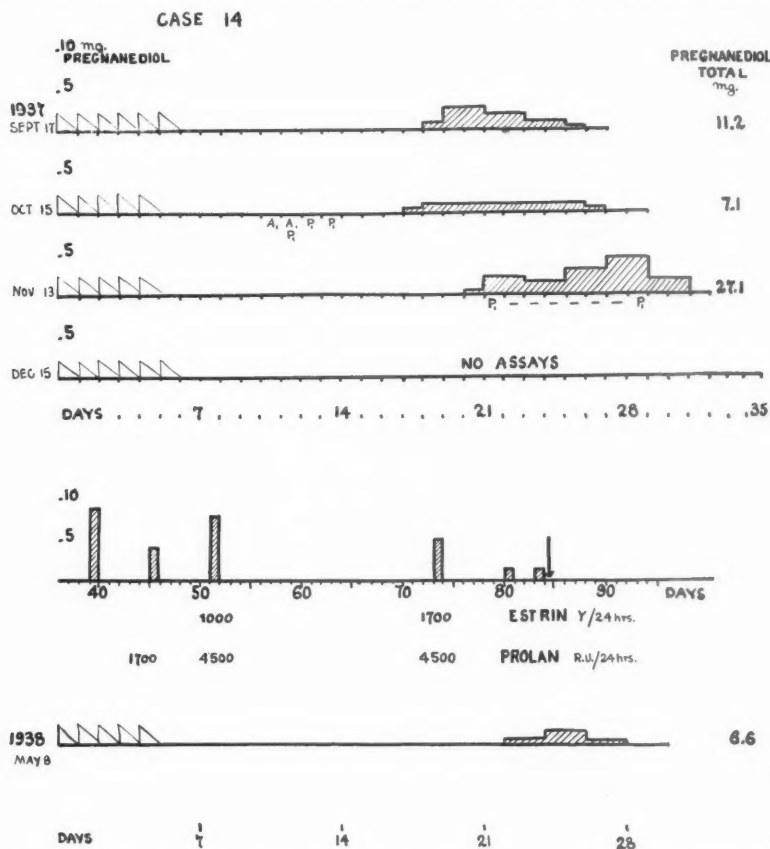


Fig. 4.—Pregnandiol, estrogen, and prolant excretion during the menstrual cycle and early pregnancy. Serrated areas represent days of menstruation. Shaded areas represent pregnandiol excretion. P, represents the injection of 100 M. U. of physex (pregnancy urine gonadotrophic extract) and A of 100 M. U. of antex (pregnant mare's serum gonadotrophic extract). The arrow marks the day on which abortion occurred.

riages in previous pregnancies), and the third those who had had one or more previous miscarriages, but who showed no abnormal symptoms during the pregnancy under investigation. The results of the assays in the first group are presented in Table II and Figs. 4 and 5. Case reports are given in detail where these are of particular interest,

otherwise in the interests of conserving space the essential facts are given in the tables or in the legends to figures.

Group I.—Patients in whom abortion actually occurred. The results of the assays in Cases 1 to 11 are shown in Table II.

CASE 4.—F. C., aged 38 years, married 8 years, gravida iii, para 0, had had an exophthalmic goiter removed in 1936, had an adolescent goiter as child, and miscarried at three months, February, 1936, at the seventy-first day in 1937, and at the seventy-first day in 1938. Progesterone was given in the last two pregnancies.

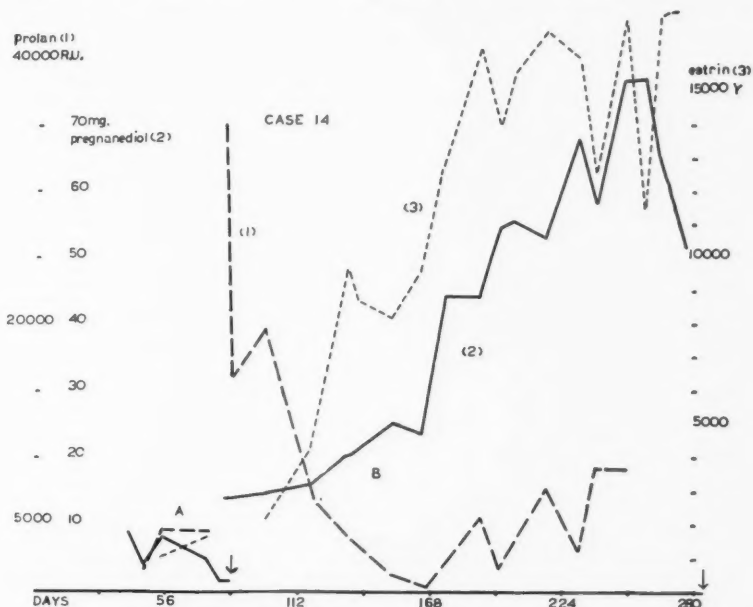


Fig. 5.—Pregnandiol, estrogen, and prolactin excretion in the same patient case as in Fig. 4. A, is the first pregnancy shown also in Fig. 4, which ended in abortion and B, is the second pregnancy which was normal throughout. In this and subsequent figures, Curve 1 represents the excretion of prolactin, Curve 2 of pregnandiol, and Curve 3 of total estrogens. The arrow marks the day on which parturition occurred, and each division on the horizontal axis is twenty-eight days.

Assays were begun in this case before symptoms commenced on the basis of the previous history. The assays showed a steady decline in pregnandiol excretion from 19.9 mg. per twenty-four hours on the fifty-third day to zero excretion on the seventieth day. The estrogen excretion was also higher than usual on the fifty-first day and declined towards the end. The prolactin was abnormally low even at the fifty-first day and fell to 500 R.U. per twenty-four hours two days after bleeding began. The value of 19.9 mg. of pregnandiol is unusually high for the period of pregnancy. This patient was found subsequently to excrete a total of 86 to 111 mg. of pregnandiol over eleven to thirteen days during the corpus luteum phase of the menstrual cycle; the highest twenty-four-hour excretion was 14.4 mg. This is an unusually high value and explains the high figure recorded here during early pregnancy.

CASE 7.—H. G., aged 24 years, had her last menstrual period on May 25, 1936. There was slight bleeding about the middle of August, that is about the eightieth or ninetieth day. There were no further symptoms until the one hundred and twenty-third day when vaginal bleeding began again. The uterus was found to be the

TABLE II.* PATIENTS IN WHOM ABORTION OCCURRED

CASE	DAY	REMARKS	PREG- NANDIOL MG./ 24 HR.	TOTAL ESTROGENS R.U./24 HR. OR GAMMA	PROLAN R.U./24 HR.
1 Aged 30 Gravida i	67	Bl.++* Pain			
	68	Bl.++ 5 mg. Pr.	0	-	300
	69	Bl.++ 5 mg. Pr.	0	-	500
	70	Bl.++	0	-	650
2 Aged 26 Gravida vi	77	Bl.+			
	84	Bl.++	-	-	55
	87-88	Bl.++			
	90		0	120	45
	93		0	330	120
	96	D. & C.			
3 Aged 26 Gravida i	81	Pain			
	82	Bl.++ 5 mg. Pr.	-	-	<500
	83	D. & C.	0	-	830
4 Aged 38 Gravida iii Para 0	53		19.9	3340x	4500
	56		17.3	3060x	1100
	57		15.6	3325x	3200
	63		11.0	2520x	2300
	66		5.9	2940x	1750
	67	Bl.+			
	68	Bl.+ 5 mg. Pr.	6.4	1600x	500
	69	Bl.+ 5 mg. Pr.	6.1	1750x	700
	70	5 mg. Pr.	0	900x	<83
	71	D. & C.			
7 Aged 24 Gravida i	80-90	Bl.+			
	123	Bl.++			
	132				
	137	Pain Bl.++ Ab.	-	17	4400
8 Aged 40 Gravida vi Para v	215		6.5	640	8800
	218		4.9	300	1700
	219		6.2	900	4200
	220-221		3.8	600	3000
	222		0.0	500	1570
9 Aged 28 Gravida iii Para ii	100	Pain. Bl.+++			
	100-106	Bl.++			
	107	Pain. Bl.++			
	107-127	Bl.+			
	120	Bl.+	26.2	3800x	5000
	124		25.8	2600x	-
	128	Fetus Ab.			
	140	D. & C.			
10 Aged 30 Gravida i	92	Bl.++			
	101	Bl.+			
	102	Bl.++			
	103	5 mg. Pr.			
	104	15 mg. Pr.			
	105	10 mg. Pr.			
	105-106		4.2	710x	2800
	107-108		5.3	900x	8300
	115		0	-	660
	146		-	-	1000
	155	D. & C.			

TABLE II—CONT'D

CASE	DAY	REMARKS	PREG-	TOTAL	PROLAN
			NANDIOL MG./ 24 HR.	ESTROGENS R.U./24 HR. OR GAMMA	
11	176		2.5	550	-
Aged 38	177	Bl.+++	4.2	200	170
Gravida vi	185		5.3	400	112
Para ii	186		5.3	500	112
	187		4.7	500	165
	188		4.9	1900	158
	189		4.9	1900	158
	190	Ab.			

*Days are counted from the first day of the last menstrual period. The significance of the symbols is as follows: *Bl.* +, slight; *Bl.* ++, moderate, and *Bl.* +++, profuse vaginal bleeding; *Pr.*, progesterone; *Op.*, operation; *Ab.*, passage of products of gestation; *D.* and *C.*, dilatation and curettage; *x.* indicates that the estrogens were done by the chemical method and are expressed in gamma, the other estrogen values are in rat units.

size of a two and one-half months' pregnancy. On the one hundred and thirty-seventh day there were cramplike pains in the abdomen. The amniotic sac contained 150 c.c. of bloody fluid; there was no embryo visible. The placenta was 10 cm. in diameter and showed necrotic changes. The assays showed a normal gonadotrophic titer for the period of pregnancy, but there was practically no estrin.

CASE 8.—A. F., aged 40 years, gravida vi, para v, one miscarriage, had been married fourteen years. Two years ago she had two months' amenorrhea; menses returned uneventfully at that time. She was admitted to the hospital Oct. 14, 1938, on the two hundred and nineteenth day. No bleeding or pain had occurred. On examination the breasts were full and a pelvic mass the size of a five months' pregnancy was felt. There was no uterine souffle, and no fetal heart sounds were heard. The pregnandiol excretion was abnormally low and fell to zero on the two hundred and twenty-second day. Estrin was also abnormally low, but the gonadotrophic titer was within normal limits. The patient did not have any abnormal symptoms in hospital; she left the hospital, and it has not been possible to learn her subsequent history. This is almost certainly, however, a case of missed abortion.

CASE 9.—H., aged 28 years, gravida iii, para ii, had her last menstrual period on Sept. 14, 1937. On the one hundredth day (December 22) severe abdominal pain and a sudden profuse discharge of blood and watery fluid from the vagina. Bleeding continued intermittently from then on, but there was no further pain until the one hundred and seventh day when it was severe. On examination the cervix was large and edematous and admitted the tip of one index finger. Uterus was the size of a four months' pregnancy. A medical induction was ordered. On the one hundred and twenty-sixth day (January 16) the patient developed a severe pharyngitis and bronchitis with a fever of 104° F. On the one hundred and twenty-eighth day the fetal cord was found prolapsed and necrotic, the fetal body was passed and the head a day later. The placenta was, however, retained for twelve more days until the one hundred and fortieth day, when it was decided to strip it off after dilatation of the cervix.

Histologic examination showed hyalinization and infarction of the placenta. The pregnandiol, estrin, and gonadotrophic excretion values done on the one hundred and twentieth and one hundred and twenty-fourth days, that is a few days before delivery of a macerated fetus, were within the normal limits for this period of pregnancy. It seems fairly certain from the history of this case that the abortion was induced.

CASE 10.—J. M., aged 30 years, married two years, had had no previous pregnancy. Her last menstrual period was on Dec. 13, 1936. Early in March she had

had German measles with high fever. On March 14 (ninety-second day) she bled enough to soil two pads and had spotted once before since having the measles, date unknown. On March 23 (one hundred and first day) there was spotting, a rather profuse flow on March 24, and she was admitted on March 25 (one hundred and third day). The uterus was the size of a three and one-half months' pregnancy. On the one hundred and third day 5 mg. of progesterone, one hundred and fourth day 15 mg., and one hundred and fifth day 10 mg. was given. She was discharged on April 3 (one hundred and twelfth day); and there has been no further bleeding. She was readmitted on May 16 (one hundred and fifty-fifth day); uterus was the size of a two and one-half or three months' pregnancy. A curettage was done on May 17. *Pathologic Report*: "Blood clot fibrin and young enmeshed ghosts of placental villi." No fetus was seen either at operation or histologic examination. Pregnanadiol and estrin excretion was low for the period of pregnancy and on the one hundred and fifteenth day the pregnanadiol fell to zero. The gonadotrophic output was, however, within normal limits for the period of pregnancy with the exception of the one hundred and fifteenth day. How much of the pregnanadiol excreted in the assay of the pooled specimens of the one hundred and fifth and one hundred and sixth days was due to the 10 mg. of progesterone injected on the one hundred and fifth day is difficult to determine. We have seen in previous cases that 5 mg. failed to cause any excretion. Injected progesterone is rapidly excreted as pregnanadiol under favorable circumstances and generally its effect on pregnanadiol excretion is all over within twenty-four hours. It is thus unlikely that the excretion on the one hundred and seventh and one hundred and eighth days was derived from this injected progesterone.

CASE 11.—H., aged 38 years, married 20 years, gravida v, para iii, miscarriage in 1937, last menstrual period April 25, 1938, was admitted Oct. 12, 1938 (one hundred and seventy-first day). Fetal movements had been absent since October 2. She was discharged on Oct. 19, 1938 (one hundred and seventy-eighth day), and readmitted on October 19, after having bled about half a pint at home. Labor was induced October 29 by gauze pack, and she delivered on October 31 (one hundred and ninetieth day). Hemorrhage and shock occurred after delivery.

The output of pregnanadiol was grossly low for the period of pregnancy, but was maintained at that low level right up to the time of delivery of the dead fetus. The total estrogen was grossly low, tending to rise slightly in the last two days. The prolan was also low unlike the other cases of abortion at this period of pregnancy.

CASE 14.—Patient, aged 23 years, married one year, had had no previous pregnancies. There was some tendency to overweight. She took thyroid from time to time for a number of years. Basal rate was -6 per cent; blood cholesterol 156 mg. per cent. Menstrual periods were regular twenty-eight to thirty days, last menstrual period occurring on Dec. 14, 1937. No abnormal symptoms until March 8 (eighty-fifth day) when there was sudden profuse bleeding and abdominal cramps. Curettage was done on March 9. The histologic section showed subinvolved necrotic decidua. No villi were seen. A second pregnancy was entirely normal throughout with the exception of slight nausea in the first few weeks. Last menstrual period occurred on July 8, 1938. Spontaneous delivery took place on the two hundred and eighty-third day. The child was normal. The results of the assays during the menstrual cycle and through the first and second pregnancies are presented in Figs. 4 and 5. They will be discussed in detail later.

Group II.—Cases showing symptoms of threatened abortion but in whom the gestation continued.

CASE 12.—L. E. H. (Fig. 6), aged 34 years, married in 1927. *First pregnancy*; last menstrual period occurred on July 20, 1936; miscarriage at sixty-two days. *Second pregnancy*: Last menstrual period occurred on Oct. 4, 1937. First abnormal symptom was bleeding on November 5 (thirty-third day); bleeding continued slightly until November 17 (forty-fifth day) with small clots on the day when she was admitted to the hospital. Bleeding still continued and on November 20 (forty-eighth

day), she was taken to the operating room. As no bleeding had occurred that morning, however, the curettage was postponed. No further bleeding occurred and the patient was sent home on December 1 (sixtieth day). She remained in bed until early in February, 1938, when it seemed from the assays that the pregnancy was progressing normally. She delivered a normal child spontaneously on the two hundred and ninety-first day. She received no progesterone at any time. The results of the assays in this case are shown in Fig. 6.

Assays were begun on the fortieth day, that is, after bleeding had been going on for a week. At this time, the pregnandiol was 11.3 mg., estrin 340 R. U., and prolan 850 R. U. per twenty-four hours. The first two values are normal, the last is low. However, on the forty-second day the prolan had risen to 14,520 units, which is normal. The pregnandiol decreased to 2.9 mg. on the forty-seventh day and to zero

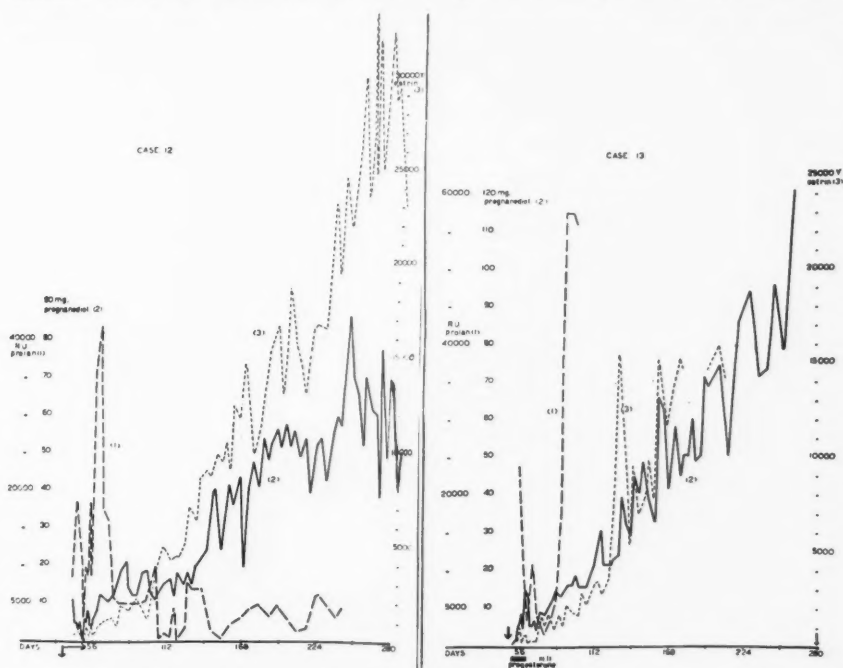


Fig. 6.—Two cases of threatened abortion. One patient had a previous miscarriage on the sixty-second day. *Case 12:* Patient had slight bleeding on the thirty-third to forty-eighth days. Thereafter there were no abnormal symptoms. Pregnan diol, estrin, and prolan fell to abnormally low levels on the forty-seventh to forty-eighth days. No progesterone was given. *Case 13:* Patient had one miscarriage at three and one-half months, and slight bleeding on the fifty-first day. Five milligrams of progesterone were given from the fifty-first to the sixty-third days. There were no further symptoms. Arrows represent the time at which bleeding occurred.

on the forty-ninth day; the estrin was zero on the forty-eighth day and the prolan less than 420 units on the forty-eighth and forty-ninth days. These assays gave the impression that the gestation had perished. On the fiftieth day, however, the pregnandiol was 6.0 mg., the estrin 700 units, and the prolan 10,000 units. Thereafter the prolan rose to the usual peak at fifty-six days, and then decreased in a normal manner and remained within normal limits throughout the rest of the pregnancy. The estrin excretion rate rose in a normal manner, a rather more rapid rise beginning about the ninety-fourth day. The pregnandiol rose to a level of between 10 and 20 mg. at about the sixtieth day and began to rise further from that level about the one hundred and thirty-fifth day. Both estrin and pregnandiol curves were within normal limits after this, the pregnandiol curve showing some fluctuations. If the possibility of confusion of specimens with some other patient on the forty-eighth and

forty-ninth days is excluded, which the authors feel can safely be done, then this case shows that a single determination showing low or even negative values, does not necessarily mean that the gestation has perished. We have seen that in the first group such low values do usually occur at this period of pregnancy in patients in whom abortion actually occurs, and in most instances do signify that the gestation is dying, particularly if they remain low on more than one determination.

CASE 13.—H. G. (Fig. 6), aged 28 years, married, gravida ii, para 0, had a miscarriage at about 3½ months two years ago. Her last menstrual period occurred on July 14, 1938. She had had severe nausea and vomiting since early in pregnancy. On September 5 (fifty-first day) there was very scanty uterine bleeding. Treatment upon admission consisted of fluids intravenously; diet. Progesterone was

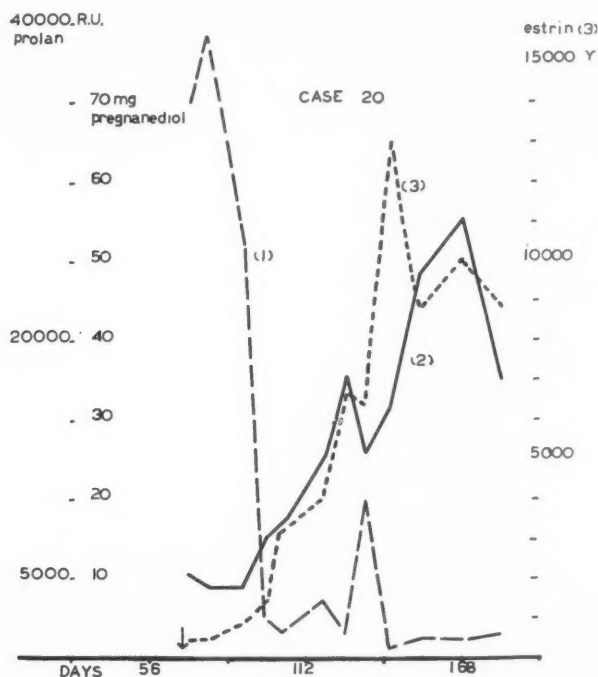


Fig. 7.—Case 20: Patient had had one previous missed abortion, with slight bleeding on the sixty-ninth day only. There were no further symptoms. Assays were normal throughout. No progesterone was given.

given, beginning with 4 mg. on date of admission (fifty-first day) and continuing with 5 mg. each day up to and including September 17 (sixty-third day). Her condition improved slowly, and she was discharged by ambulance September 23 (sixty-ninth day). There was no further bleeding, and she delivered a normal child on April 20, two hundred and seventy-ninth day. The results are shown in Fig. 6.

On the fifty-second day the pregnandiol was 2.3 mg., an abnormally low value, in spite of the injections of 5 mg. of progesterone mentioned above. The rate of excretion was between 5 and 8 mg. from the fifty-third to the fifty-eighth day, rising to 15.0 mg. on the fifty-ninth and sixtieth days, and falling to 8.0 mg. on the sixty-first day. It declined further to 5 or 6 mg. on the sixty-fourth day after the cessation of the progesterone injections. On the seventy-third day, in view of the decrease in pregnandiol to 4.1 mg. on the sixty-eighth day, 5 mg. of progesterone were given and repeated on the seventy-fourth, seventy-fifth, seventy-seventh, eighty-ninth, and ninety-first days. The fall in pregnandiol was only temporary, however, and it

probably was unnecessary to give the progesterone. The pregnandiol excretion began to rise from this level about the seventy-ninth day, a normal time for the increase to occur, and rose steadily in a normal manner throughout. The total estrogens were perhaps a little low at first, but rose parallel to the pregnandiol with some fluctuations. The determinations in the latter part of pregnancy have not been completed. The prolان curve showed a high point of 30,000 units on the fifty-fourth day, then a series of lower values and a second rather unusually late peak of 50,000 units on the eighty-fifth, eighty-ninth, and ninety-third days.

CASE 20.—(Fig. 7.) Patient, aged 24 years, had a missed abortion in 1936. Symptoms began at the one hundred and sixty-fifth day when the uterus was the size of three or three and one-half months' pregnancy. *Second pregnancy:* Last menstrual period occurred on Sept. 8, 1937. She bled slightly on the sixty-ninth day, and there was no further bleeding. Labor occurred on the two hundred and eighty-first day, and the child was normal. The assay results are shown in Fig. 9.

The excretion rate of prolان, estrogens, and pregnandiol was normal throughout, except a slight decrease in excretion of pregnandiol and estrogens about the one hundred and eighty-second day. After this time no assays were done. Labor was normal and at term.

CASE 27.—Ea., aged 31 years, last menstrual period June 28, 1937, had slight bleeding in early August. On September 12 to 18 she passed a moderate amount of dark blood; there was no pain and no further symptoms. She delivered normally on the two hundred and seventy-seventh day. No progesterone was given. Assays given in Table III show normal values for pregnandiol and estrogens and a rather high value for prolان.

TABLE III. PATIENTS IN WHOM ABORTION THREATENED

CASE	DAY	REMARKS	PREGNANDIOL MG./24 HR.	TOTAL ESTROGENS R.U./24 HR. OR GAMMA	PROLAN R. U./24 HR.
27	76-82	Bl.+			
	88		15.9	1,050	83,000
	89		14.3	800	30,000
28	41	5 mg. Pr.			
	43	5 mg. Pr.	4.6	154	102,000
	44	5 mg. Pr.	4.6	154	102,000
	45	5 mg. Pr.	5.4	179	116,000
	46	-	5.4	179	116,000
	47	5 mg. Pr. Bl.+	4.4	150	24,000
	48	5 mg. Pr. Bl.+	4.4	150	24,000
	49	-	5.2	240	30,000
	50	5 mg. Pr.	5.2	240	30,000
	51	5 mg. Pr.			
	53	5 mg. Pr.			
	55	5 mg. Pr.			
	57	5 mg. Pr.	9.2	450	50,000
	58	5 mg. Pr.			
	60	5 mg. Pr.	9.3	450	110,000
	67	-	10.3	550	83,000
	71	-	7.7	550	
	78	-	11.5	830x	
	81	-	11.7	1,700x	
31	97	Pain	10.4	980x	11,000
	103		4.6	840x	-
	104		3.4	-	-
	106		7.0	1,870x	-
	108		8.5	2,840x	-
	128		14.6	4,400x	-

x. Indicates that the estrogens were done by the chemical method and are expressed in gamma; the other estrogen values are in rat units.

CASE 28.—Fa., aged 30 years, married seven years, gravida ii, para 0, had her last miscarriage in 1936 at three months, preceded by brownish discharge. Her last menstrual period was on Jan. 24, 1939. The first abnormal symptom appeared on the forty-first day, consisting of brownish discharge. She was put to bed, and was given 5 mg. of progesterone daily from the forty-second day to the forty-fifth day and every other day from then until the fifty-eighth day. No further bleeding occurred after the forty-eighth day.

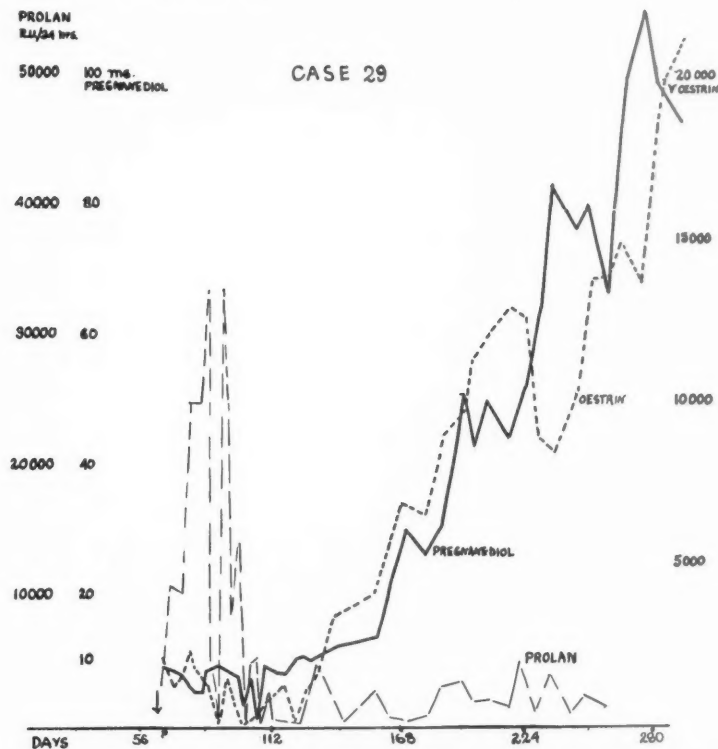


Fig. 8.—Case 29: Patient had had two previous miscarriages, one in the second month and one in the third month. There was slight bleeding on the sixty-ninth and seventieth days. Five milligrams of progesterone were given on the seventy-first and seventy-second days and vitamin E thereafter. She was kept in bed until about the one hundred seventy-fifth day. There were no further abnormal symptoms. Pregnanediol and estrin values fell to abnormally low values about the one hundred twelfth day. Up to about the one hundred fiftieth day, the pregnandioli excretion rose but slightly above the level of 10 mg. per twenty-four hours. Thereafter it rose rapidly to high normal values. Estrogens began to rise about twenty-eight days before the rise in pregnandioli occurred.

The assay results are shown in Table III. The pregnandioli values are perhaps a little low if one considers the daily injections of progesterone until about the fifty-seventh day; but the actual values are within normal limits. The estrogen values are normal and the prolan excretion shows a high peak from the forty-third to forty-sixth days and another high point about the sixtieth day. On the eighty-first day which is the last assay completed, the estrogen excretion is beginning to show the rise usually occurring at this time of pregnancy. There is nothing in these assays to differentiate them from those of a normal pregnancy.

CASE 29.—J. R. (Fig. 8), aged 32 years, married six years, gravida iii, para 0. *First pregnancy*: Miscarried in November, 1935, at about seven weeks. *Second pregnancy*: Last menstrual period on Aug. 16, 1936; first abnormal symptom bleed-

ing on October 31 (seventy-seventh day). She was admitted on November 1; 5 mg. of progesterone was given on November 2 and 3; on November 4 dilatation and curettage, no fetus was seen. *Pathologic report*: "Decidua compacta and spongiosa with few necrotic young villi." This was followed by acute endometritis with onset on November 16, twelve days postoperative. *Third pregnancy*: Last menstrual period Jan. 9, 1938 (approximately); slight spotting on February 4 (twenty-seventh day). There was slight bleeding on March 18 and 19 (sixty-ninth and seventieth days). She was admitted March 19, given 5 mg. of progesterone on March 20 and 21, and discharged on March 23. The patient was kept in bed until July, and given vitamin E (Horner). She was delivered Oct. 24, 1938 (294th day) of a normal child.

The prolactin values were irregular in the first part of the pregnancy. Both estrogen and pregnandiol values fell to abnormally low values about the one hundredth day, though there were no symptoms at this time. The striking feature of the pregnandiol curve was the very late period at which it begins to rise above the level characteristic of early normal pregnancy. It was not until about the one hundred and fiftieth day that a significant rise occurred. After the one hundred and sixtieth day it was rapid and reached high normal values before the end of pregnancy. The rate of excretion of estrogens began to rise about twenty-eight days before that of pregnandiol, and also followed a normal course thereafter.

CASE 31.—Wi. had two miscarriages in 1935 at three months. Her last menstrual period occurred on Aug. 26, 1936. On the ninety-seventh to one hundred and tenth days there was pain in the back and abdomen, no bleeding, and the pregnancy proceeded normally to term. The prolactin titer (Table III) on the ninety-eighth day was normal. Estrogen excretion was also normal. Pregnanediol excretion fell from 10.4 mg. on the ninety-seventh day to 3.4 mg. on the one hundred and fourth day and rose again to 14.6 mg. by the one hundred and twenty-eighth day. It is questionable whether this should be regarded as a threatened abortion.

Group III.—The third group of cases comprises those patients who had had one or more miscarriages in previous pregnancies, but who showed no abnormal symptoms during pregnancy under investigation.

CASE 22.—W. M. (Fig. 9) had had two previous miscarriages; one occurred in 1936 at six months; symptoms began at three months; the second miscarriage occurred at three months in 1937. *Third pregnancy*: Last menstrual period on Sept. 21, 1938. No abnormal symptoms had occurred during the present pregnancy. The assay values were normal throughout. Injections of 5 mg. of progesterone were given as indicated in the figure from the eighty-sixth to the one hundred and tenth day as a precautionary measure; but this was probably entirely unnecessary.

CASE 23.—U. (Fig. 9) had had one normal pregnancy, and also had had a miscarriage in 1935 at four months, and in 1937 at two months. Her last menstrual period occurred on Sept. 11, 1938. There were no abnormal symptoms. The excretion of prolactin and estrogens was normal, but an unusually low amount of pregnandiol was excreted from the sixty-second day (when assays began) to the eightieth day (1.0-4.9 mg./24 hr.); 9 mg. of progesterone were given daily on the eighty-first to the eighty-fourth days; the level of pregnandiol rose slightly during the injections; a level of 13 to 15 mg. was maintained from the ninety-sixth to the one hundred and fifty-fourth day. After this the value rose to 30 mg. about the one hundred and eightieth day; it was still definitely lower than the usual normal value for this period of pregnancy.

CASE 26.—R. A. (Fig. 10) had had one previous miscarriage at three months. Her last menstrual period was Aug. 13, 1938. The prolactin values around the sixtieth day are perhaps somewhat lower than normal, being 14,000 units. On the seventy-fourth day only 700 units were excreted, and the pregnandiol value dropped to 2.3 mg. from 5.2 mg. on the sixty-seventh day. At this time it was thought from the

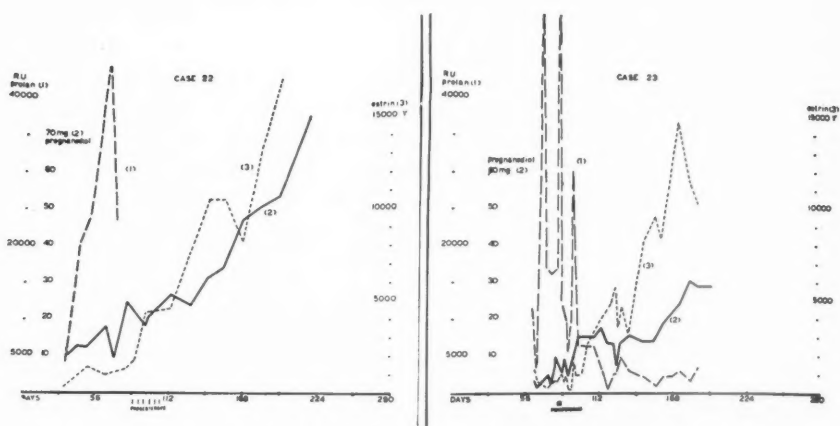


Fig. 9.—Case 22: Patient had had two previous miscarriages, one at six months (symptoms began at three months) and the second at three months. There were no abnormal symptoms during the present pregnancy. The assay values were normal throughout. The progesterone given in 5 mg. doses as indicated was probably unnecessary. Case 23: Patient had had two previous miscarriages at four months and at two months. There were no abnormal symptoms during the present pregnancy. Excretion of prolan and estrogens was normal, but pregnandiol was abnormally low in the early part of pregnancy and failed to rise to the normal level even at the one hundred eightieth day. Progesterone 9 mg. daily was given from the eighty-first to eighty-fourth day.

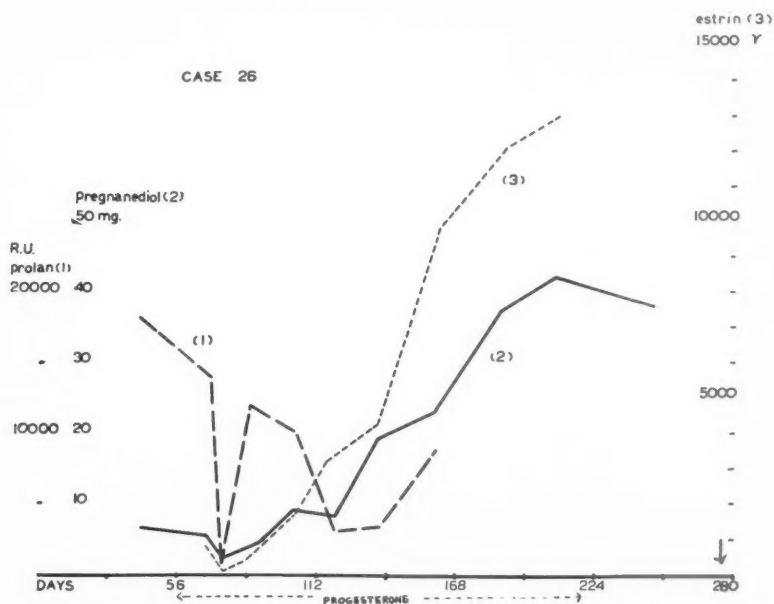


Fig. 10.—Case 26: Patient had had one previous miscarriage at three months. There were no abnormal symptoms in the present pregnancy. On the seventy-fourth day, 700 units of prolan and 2.3 mg. of pregnandiol were excreted. It was suspected that the gestation was dying, but the pregnancy continued normally and the excretion of estrogen began to rise about the one hundredth day and a definite rise in pregnandiol began about the one hundred and twelfth day; 1 mg. of progesterone was given three times weekly from the fifty-sixth to the one hundred eighteenth days and 1 mg. twice weekly from the one hundred and eighteenth to the two hundred and tenth days.

assays that the gestation had perished. However, on the one hundred and first day, the pregnandiol was 9.4 mg. and the prolan 10,000 R. U. and on the one hundred and thirty-fourth day the fetal heart was heard. The pregnandiol excretion rose to 19.3 mg. by the one hundred and thirty-seventh day and was about 40.0 mg. on the one hundred and eighty-fifth, two hundred and seventh, and two hundred and forty-eighth days, which is lower than usual. The total estrogen excretion was more or less normal throughout. One milligram of progesterone was given three times weekly from the fifty-sixth to the one hundred and eighteenth day, and 1 mg. twice weekly from the one hundred and eighteenth to the two hundred and tenth day. It is difficult to estimate the effect of this relatively small amount in preventing the occurrence of symptoms. Labor was induced on the two hundred and seventy-fourth day and a normal child was born.

CASE 32.—Co. had had several miscarriages on previous occasions at the third month. She was receiving 1 mg. of progesterone daily up to the seventy-fifth day. The assays were requested as a guide to the necessity for further therapy. As seen from Table IV, the assay values were normal for the period of pregnancy, and on

TABLE IV. PATIENTS IN WHOM ONE OF MORE PREVIOUS PREGNANCIES HAD TERMINATED IN ABORTION BUT WHO SHOWED NO ABNORMAL SYMPTOMS DURING THE PREGNANCY UNDER INVESTIGATION

CASE	DAY	REMARKS NUMBER OF MISCARRIAGES	PREGNANDIOL MG./24 HR.	TOTAL ESTROGENS R.U./24 HR. OR GAMMA	PROLAN R.U./24 HR.
32	75	Several	16.3	555	71,500
	83		29.1	600	--
33	63	1	18.3	--	64,800
	87		25.6	1,500x	28,220
	100		28.5	1,330x	22,100
34	51	2	8.8	--	5,500
	56		9.1	--	6,600
	72		17.6	655	2,200
	89		19.4	--	--
	125		28.0	--	3,000
35	40	1	7.8	840	1,150
	50		10.1	1,980	15,000
	57		10.1	1,105x	17,400
	65		11.0	1,400x	112,000
	72		11.6	1,140x	63,000
	78		13.5	3,020x	41,000
	85		11.3	1,990x	14,600
	88		14.7	1,170x	32,400
	93		12.2	2,465x	8,000
	100		12.3	1,760x	9,000
	106		12.2	3,220x	
	114		13.0	1,920x	6,000
	121		17.7		2,950
	127		20.8		
	135		26.8		1,700
	141		25.8	9,110x	
	155		28.4		8,525
	163		41.6		2,420
	169		49.6		11,880
	177		45.3		
	183		58.8		
	191		58.0		
	198		70.1		
	205		82.4		

x, Indicates that the estrogens were done by the chemical method and are expressed in gamma, the other estrogen values are in rat units.

repeating the assay on the eighty-third day, the pregnandiol had risen to 29.1 mg., which is a high normal value. Advice was given that no further progesterone was necessary.

CASE 33.—D. had had one miscarriage at the third month. Her last menstrual period occurred on July 27, 1928. The assays shown in Table IV are within normal limits. There were no abnormal symptoms during the pregnancy.

CASE 34.—J. had had previous miscarriages at the fifth and tenth weeks. Her last menstrual period occurred on Dec. 2, 1936. There were no abnormal symptoms in this pregnancy which proceeded normally to term. The assays shown in Table IV show a normal excretion of pregnandiol which begins to rise from the level of early pregnancy at the normal time. The prolactin excretion was rather low for the fiftieth to sixtieth day.

CASE 35.—T., aged 29 years, married four years, had had one miscarriage in the third month. Her last menstrual period occurred on September 25, 1938. There were no abnormal symptoms. The assay values (Table IV) are essentially normal. The time of the rise in pregnandiol excretion above the level of 12 mg. is perhaps somewhat delayed. It does not begin until the one hundred and twenty-first day.

DISCUSSION

In the first group Cases 1 to 4 and Case 14 are spontaneously occurring abortions in the early part of pregnancy. In Cases 1 to 3 the assays were begun only after symptoms had occurred. The pregnandiol is negative in 3 cases and low in the fourth, and the prolactin is abnormally low in all of them. In connection with the decision as to what is a normal prolactin value, comparison should be made with the values set forth in Fig. 3 and Table I. From these it is obvious that what would be a normal level for prolactin in the sixth month, for example, would be definitely abnormal in the late second and early third months when the normal high peak of excretion occurs. In Case 6 the assays were done eight days before the actual abortion which may account for pregnandiol still being present. In Case 4 assays were started fourteen days before the onset of symptoms and at that time showed a low prolactin with high estrin and pregnandiol. These high values are explained, as has been mentioned, by the character of the corpus luteum in this individual. It secretes unusually large amounts of progesterone even in the menstrual cycle. Progesterone in 5 mg. doses, started after symptoms commenced, failed to influence the course of events. In these cases the gestation was obviously degenerated before the onset of symptoms. Case 14 may be discussed in more detail. In Fig. 4 are seen the assays of pregnandiol in the menstrual cycles; they are abnormally low, even the injection of pregnancy urine gonadotrophic extract fails to raise the excretion to the normal level. One may speculate as to the cause of abortion in this case. First, it is possible that the low pregnandiol excretion in the menstrual cycles was a reflection of an inadequate corpus luteum, that this indicated an abnormal follicle and so, conceivably an abnormal ovum. Second, the fertilized ovum may have been normal, but assuming that the corpus luteum in the cycle during which conception took place was as poorly functioning as in the other cycles, then satisfactory progestational

transformation of the endometrium may have failed to take place, so that while the ovum did implant it failed to develop normally. It will be seen that in the early part of the gestation (forty to fifty days) the pregnandiol excretion was normal. The prolactin excretion, however, failed to rise, remaining at 4,500 units. This may reflect the failure of the chorion to develop normally in an abnormal gestation due to either of the above causes or to any other cause. In this connection one may compare the case of ectopic gestation previously reported in which a fall of urinary prolactin excretion took place with each new hemorrhage into the gestation sac.⁶ Since we have seen that as the corpus luteum grows older it probably needs increasing gonadotrophic substance to keep it functioning, after about the seventy-fifth day in this case the 4,500 units failed to maintain the corpus luteum and it began to degenerate as shown by the decrease in pregnandiol excretion, and abortion occurred. This case illustrates clearly the course of a gestation, which from the prolactin excretion and the histological findings at the time of abortion, failed to develop normally from a very early stage, though symptoms did not occur until much later. The onset of symptoms may be determined by the endocrine relations described above. It is obviously futile to treat such a case with progesterone or anything else at the time the symptoms appear. On the second hypothesis advanced above it might have done some good to treat the patient with progesterone during the luteal phase of the menstrual cycle, but this is hardly practicable. After the first pregnancy another assay in the menstrual cycle showed the same low findings. The second pregnancy (Fig. 5, B) proceeded entirely normally; whether this was due to the occurrence at intervals of a normal corpus luteum in this individual, which would provide an adequate implantation site and would persist long enough for the placenta to take over the formation of progesterone, or to the existence of a normal fertilized ovum in the second pregnancy is purely speculative. In Case 4 one would have to assume a faulty germ plasma reflecting itself in a poorly developed chorion which produced an amount of prolactin inadequate to maintain the corpus luteum, since in this case the pregnandiol and estrin excretion were high. The fifth case, not reported in detail here, illustrates the effect of removal of the corpus luteum at the fifty-second day of gestation. Four days later pregnandiol was negative and the prolactin was definitely low, falling to 55 units ten days after the operation and abortion followed. In the case of Jones and Weil,²⁴ the patient was operated upon at the fifty-eighth day and pregnandiol persisted for three days postoperatively; on the fifth to twelfth day it was negative, and then reappeared and by the one hundred and thirty-sixth day of pregnancy had reached a normal level and pregnancy continued to term. This negative period indicates according to these authors that pregnancy may persist at least for a short time without progesterone or at least with minimal amounts. This is of interest in view of the temporarily negative finding in a case of threatened abortion reported in this paper. On the other hand we know that factors such as the glucuronic acid conjugation

mechanism, etc., may affect excretion of pregnandiol even when progesterone is being produced, so that a negative pregnandiol does not necessarily mean absence of progesterone from the body. Numerous other cases have been reported in which the corpus luteum has been removed at or before this period of pregnancy and the pregnancy has carried to term.

Case 8 is of interest since it presents the findings in a case of induced abortion. In this case in spite of the bleeding, the assay values are entirely normal for the period of pregnancy. Four days after the last assay the fetus was delivered in a macerated condition, but it will be noted that the placenta remained firmly attached and had to be removed sixteen days after the last assay. This shows clearly that the fetus is not the source of the hormones excreted in the urine, more particularly that the fetal adrenal is not the source of the pregnandiol. It also illustrates that if a gestation has developed normally and the fetus is killed by outside interference the placenta continues to function at least for a time. This is unlike those cases in which the death of the fetus is due to an abnormality which affects both fetus and placenta. Frank,²⁹ in an intrauterine full-term pregnancy in which the placenta had been left for eighteen days after delivery, found the blood estrin still high, and Ware and Main,³⁰ in an intra-abdominal pregnancy at term, found that prolan persisted in the urine for about a month.

Cases 7, 8, 10, and 11 are missed abortions occurring later in pregnancy. The striking feature in them (except in Case 11) is that the prolan values are entirely normal for the period of pregnancy, unlike the cases of abortion completed early. The excretion of pregnandiol and estrogens on the other hand is grossly low. In Case 7 the gestation ceased to develop presumably at the time of the first symptom (eighty to ninety days), in Case 8 the time of cessation of development is unknown but was probably after the fifth month, in Case 10 probably at the time of the first symptoms at the one hundred and fifth day, and in Case 11 possibly on the one hundred and sixty-first day. On this basis then the assays were done in Case 7 about fifty days, in Case 8 about two months, in Case 10 at the time and ten and forty days, and in Case 11, fifteen to thirty-eight days after the cessation of development of the gestation. The assay findings probably depend upon the time in pregnancy at which the gestation ceased to develop and the length of time which had elapsed before assays were done as well as upon the degree of degeneration which had occurred in the placenta. It may be said that the placenta (chorion) begins to form prolan before it begins to form estrogens and progesterone. If the gestation ceases to develop before the placenta has begun to form these substances to any extent as in Cases 7 and 10, then apparently it seems not to go on to develop that function, or if it does, loses it before the time of assay in these cases, even though it remains in contact with the maternal circulation and continues to secrete prolan. If as in Cases 8 and 11 cessation of development occurs later in pregnancy, assuming that they were normal up to that time, the placenta

had by that time begun to form estrogens and progesterone and these substances continue to be excreted for some time though in smaller quantities than normal. In Cases 8 and 10 it is seen that pregnandiol may become negative in the urine without abortion occurring immediately, and in Case 11 abortion occurred while pregnandiol was still being excreted.

In the second group are included the cases of threatened abortion. It is in these cases that the difficulty of determining the effect of various forms of therapy arises. In this and the next group are included cases which fall into the class of habitual abortion. We shall limit ourselves here to discussion of the endocrine factors which we believe to be involved in the causation of symptoms in these cases, clearly recognizing, however, that there may be numerous other factors operating. We believe that the endocrine factors are in many instances the final common pathway upon which these other influences exert their effect.

Cases 12 and 13 (Fig. 6) may be compared; both patients had had one previous miscarriage, both had slight symptoms in the second month, in both the pregnandiol fell nearly to zero over one or two days at the time of the symptoms. The patient in Case 12 received no progesterone, patient in Case 13 received 5 mg. daily for twelve days. In both of these patients pregnandiol and estrogens rose after the period of symptoms to normal levels, rather more slowly in Case 12. The prolactin in both patients fell to abnormally low values, for one day in Case 12 and for a short period after symptoms had ceased in Case 13. This together with the results in Cases 23, 26 and 29 shows that a temporarily low or even negative value for pregnandiol excretion and a low value for prolactin excretion at this period of pregnancy are not incompatible with continuance of pregnancy to term. In some of the cases no symptoms accompany these low values. They tend to occur at a time when the transfer of function is taking place between the corpus luteum and the placenta, as the site of formation of progesterone. It is, however, difficult to account for the low prolactin values on this basis. In the patient in Case 17 the bleeding which occurred at irregular intervals came in all probability from the eroded cervix. In this patient the assay values were normal in the early part of pregnancy, the estrin was normal late in pregnancy, but the pregnandiol was somewhat low. The patient was slightly toxic later in pregnancy, and this may account for the low pregnandiol values since it has been shown by Weil,³¹ Browne, Henry and Venning¹¹ and Smith and Smith²⁵ that low values are found in many cases of toxemia in late pregnancy. This case illustrates the necessity for considering the possibility that bleeding during pregnancy is not always threatened abortion and of excluding such cases when considering the effect of therapy on this condition.

The very slight symptoms in the patient in Case 20 perhaps do not justify inclusion as one of threatened abortion. The assays were entirely normal throughout. The patients in the cases in Table III are

others with normal or temporarily slightly low pregnandiol and normal estrogens and prolan in whom symptoms occurred and who carried to term.

In Table IV are shown 4 patients who had miscarried in previous pregnancies. Only one (Case 32) received progesterone in 1 mg. doses up to the seventy-fifth day. All showed entirely normal assay values with the rise in pregnandiol excretion occurring at the usual time. The patient in Case 26 had had one previous abortion and showed no symptoms in the present pregnancy. In spite of this the pregnandiol and prolan assays were very low at the seventy-fourth day and the rise in pregnandiol began a little late, and remained low throughout the rest of pregnancy. Case 22 and 23 are both patients who had had two previous miscarriages; in the patient in Case 22 the values were entirely normal throughout, and the progesterone was almost certainly unnecessary. In Case 23 the pregnandiol values were low and the rise in pregnandiol delayed.

There are then some patients who have aborted in a previous pregnancy or pregnancies, including cases of repeated or habitual abortion, in whom a subsequent pregnancy may be entirely normal from all points of view. There are others who may or may not have symptoms in whom the pregnandiol assays and sometimes the prolan assays are low at the critical period of pregnancy and in whom the normal rise in pregnandiol excretion takes place later than usual and may fail to rise to the usual level late in pregnancy.

Based upon the considerations discussed in the introduction and upon the findings in the cases reported here, the following theory of the endocrine mechanism of threatened and habitual abortion may be outlined. It has been previously discussed by Browne and Venning,⁶ and parts of it have been suggested by many investigators. Experimental evidence with regard to the metabolism of progesterone in human pregnancy has, however, been lacking hitherto, and consequently the theory has lacked basis.

As stated in the introduction, the evidence suggests that there are two sources of progesterone and estrogens in pregnancy in the human being. These are the ovary with corpus luteum and the placenta. We interpret the rise in pregnandiol excretion which occurs about the seventieth to ninetieth days in most normal cases, as being due to the beginning of secretion of progesterone by the placenta. It was previously thought that, since the corpus luteum degenerates in many instances about the third month and since the ovaries could be removed and pregnancy continue, progesterone was unnecessary in the latter part of human pregnancy. This view is no longer tenable. Whether all the pregnandiol in late pregnancy is derived from progesterone and what is the minimum level necessary for maintenance of pregnancy is unknown. The time at which the transfer of function occurs from ovary to placenta varies in different individuals and in the same individual in different pregnancies. If, however, the corpus luteum ceases to produce progesterone for any length of time before the placenta begins to secrete it, abortion will follow. The time at

which a deficiency of corpus luteum hormone is most likely to occur is therefore in the transition period between the ovarian and placental phases (late second and third months); this is the critical period of pregnancy. It has been recognized for a long time that abortion tends to occur most commonly at this period. Henry and others³² studied the distribution of time of onset of symptoms in 500 cases of abortion (threatened, complete, and incomplete) and found the average day to be the eighty-first from the beginning of the last menstrual period.

As we have seen, some corpora lutea are more readily maintained by pregnancy urine extracts than others, and this may also be true with regard to the maintenance of the corpus luteum by chorionic gonadotrophic substance in early pregnancy. The cause of many abortions as mentioned is a faulty gestation from the first; the chorion partakes in this abnormality and produces an amount of gonadotrophic substance inadequate to prolong the corpus luteum beyond a certain point. In other patients where the gestation is less abnormal, the function of the corpus luteum may be prolonged for the usual time and the embryo develop normally, but the placenta may be slow in taking over. In either case abortion follows. Patients in whom either of these conditions repeatedly occurs habitually abort. We have noted several patients in whom the rise in pregnandiol occurs very late, for example Case 29 (Fig. 8). This patient had had two previous abortions and threatened to abort in the pregnancy under investigation. The pregnandiol did not rise above the level characteristic of the corpus luteum phase until very late. Ordinarily the corpus luteum degenerates at about the third month. It has, however, been shown by Tietze and Wegener³³ that in some cases the corpus luteum may be histologically normal up to term. It seems a possible explanation that on this occasion the patient in Case 29 had such a corpus luteum which produced enough progesterone to carry her until the placenta took over. Incidentally this case shows that the minimum amounts necessary for maintenance of pregnancy are considerably below those usually present. The occasional persistence of a functioning corpus luteum beyond the usual time may explain some of those patients who abort several times and in a subsequent pregnancy carry through to term. It is, of course, equally possible in the patient in Case 29 that the placenta did begin to take over the function of forming progesterone at the usual time and that the low values for pregnandiol, seen about the one hundredth day, occurred at the time of cessation of function of the corpus luteum. The fall in the rate of prolan excretion which occurred at this time would agree better with this explanation on the theory⁶ that this fall occurs when the placenta begins to utilize prolan within itself. If the placenta did begin to form progesterone about the one hundredth day in this patient, then the amount which it formed remained low until the one hundred and fiftieth day. The patient in Case 23 who had miscarried on two previous occasions shows this slow rise in pregnandiol, even though there were no abnormal symptoms in the pregnancy investigated. This may indicate that in some cases of repeated abortion

the placenta repeatedly fails to take over its function satisfactorily. On the other hand we have seen that other patients who had aborted in one or more previous pregnancies show entirely normal curves of pregnandiol excretion which rise from the level characteristic of the corpus luteum phase of pregnancy at the normal time.

With regard to therapeutic use of progesterone, pregnancy urine extracts, vitamin E, etc., in the treatment of threatened and habitual abortion, numerous claims for good results have been made. The present study shows how difficult it is to evaluate the results of such therapy. The use of gonadotrophic extracts where such large amounts are present as in early pregnancy seems likely to have little effect. In those patients where the prolactin excretion is consistently low, we have seen in most cases the gestation is already degenerate. Good results from the use of progesterone have been reported by Hall,³⁴ Bishop, Cook and Hampson,³⁵ Krohn, Falls and Lackner,^{36, 37} Kane,³⁸ Clauberg,³⁹ Gershenfeld,⁴⁰ Elden,⁴¹ and others. In most instances the amounts of progesterone used have been very small: of the order of $\frac{1}{25}$ of a rabbit unit to 1 rabbit unit per dose with the doses given daily to weekly. This has been due in part to the difficulty in obtaining larger amounts of the material at least until recently, and to its high cost. In those patients with abortion in whom the gestation is degenerate before the onset of symptoms, progesterone is obviously useless given when symptoms appear. A large proportion of these are abnormal from the first, and even if therapy is started before symptoms appear, the result will be unsatisfactory. The patients in whom the embryo and placenta develop up to a certain period, but the placenta takes over the function of progesterone formation late or the corpus luteum degenerates early, offer theoretically the most hopeful outlook for progesterone therapy, since in many, if the critical period can be tided over, the placental function begins and further therapy is unnecessary. It is possible that the determination of prolactin excretion in early pregnancy may enable one to distinguish patients in whom the gestation is already degenerate from those in whom therapy might be of benefit. However, as shown in this investigation, a single determination is of no value, since patients showing temporary low prolactin values in early pregnancy, do carry through to term.

In view of the fact that patients who have aborted once and even those who have aborted more than once (without obvious explanation) and thus fall into the category of habitual abortion may yet in a subsequent pregnancy proceed entirely normally, as far as absence of symptoms and normality of endocrine assays are concerned, it is very difficult to estimate the value of progesterone in this group. Theoretically one should give the progesterone before the time of usual onset of symptoms and continue it over the critical period. The question of dosage is also difficult to determine. From the pregnandiol assays, it seems obvious that the amount of progesterone produced by the corpus luteum up to the seventieth or eightieth day is 5 to 10 mg. per day, and that the placenta produces a gradually increasing amount as pregnancy advances. How much is the minimum requirement is

unknown. It is also unknown unless determinations are made how much the patient's own endocrine organs are producing, so that one may be giving 1 mg. of progesterone to a patient in the fourth or fifth month, when she is producing 25 to 50 mg. herself. In any case, it would seem, in view of the above findings, that doses of less than 5 mg. are unlikely to have much effect. This dose should be given daily, or every other day, and may be increased in the presence of persisting symptoms. In most cases either of the threatened or habitual type, therapy should be concentrated during the period of transfer of the function of formation of progesterone from ovary to placenta, since it is at this time that abortion is most likely to occur. If pregnandiol assays are available, a definite rise in pregnandiol excretion may be taken as an index that further therapy is probably unnecessary. The danger of wasting treatment on an already dead fetus, and the uselessness of treating a patient after her own placenta has begun to form normal amounts of progesterone, should always be borne in mind.

SUMMARY

1. The physiology of normal pregnancy is discussed from the point of view of the endocrine factors involved.

2. A study has been made of 35 cases of threatened or habitual abortion, and measurement of the excretion of prolan (chorionic gonadotrophic substance), total estrogens and sodium pregnandiol glucuronide has been made in twenty-four-hour specimens of urine in these patients for varying lengths of time, in some patients throughout pregnancy.

3. A theory of the underlying endocrine basis for abortion is presented.

4. An attempt is made to evaluate progesterone therapy in such cases on a rational basis.

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DISCUSSION

DR. JEAN PAUL PRATT, DETROIT, MICH.—My assistant, Dr. Stover, has assayed the urine in our abortion cases during the past year. Using the same method as Browne, similar results have been obtained. The method is satisfactory in that it has a sharp end point. Pure crystals of pregnandiol glucuronide are obtained and the melting point determined.

The average curve of excretion of pregnandiol during menstruation and normal pregnancy is established with reasonable satisfaction. It is noteworthy, however, that a wide variation exists in the individual readings for hormone excretion. The difference amounts to as much as 300 per cent in pregnandiol, 500 per cent in total estrogens, and is even greater in prolan. The same individual varies widely from day to day, and different individuals of course vary. It is evident, therefore, that one cannot wisely interpret single or even a few assays as abnormal. Seven of Browne's patients and four of ours presenting symptoms of abortion, showed low assays of pregnandiol but progressed to full term. Three of his cases and one of ours had no symptoms of abortion but showed low assays of pregnandiol.

I agree with the assumption that there are two sources of progesterin in the human body, the corpus luteum and the placenta. Browne is justified in his interpretation that the rise in pregnandiol excretion, which occurs about the seventieth to ninetieth day in most normal pregnancies, is due to the beginning of secretion by the placenta. I cannot agree with the assumption that if the corpus luteum ceases to produce progesterin for any length of time before the placenta begins to secrete it, abortion will follow.

In one case I reported in 1927 (*Endocrinology* 11: 195, 1927) the corpus luteum of pregnancy was removed on the twentieth day, but the patient continued through a normal pregnancy and delivered an eight-pound baby on the two hundred and seventy-second day after her last menstrual period began. The corpus luteum removed was found to be normal histologically. This patient was deprived of her corpus luteum before chorionic tissue developed to continue the secretion of progesterin. If progesterin is essential to the continuance of pregnancy, there must have been some other source, in this instance, than either the corpus luteum or the placenta.

Several cases are reported in the literature in which the ovaries were removed too early for the chorionic tissue to secrete progesterin. Douglass (*Surg. Gynec. Obst.* 52: 52, 1931) removed the corpus luteum in the fourth week, but the pregnancy continued to term. Corbet (*Irish J. M. Sc.* p. 520, 1932) removed the corpus luteum on the forty-second day without abortion. Unfortunately these patients were observed before pregnandiol excretion was being assayed.

Jones and Weil (*J. A. M. A.* 111: 519, 1938) removed the corpus luteum on the fifty-eighth day. Pregnanadiol decreased to 0 on the sixth postoperative day and reappeared on the fourteenth day. Two explanations may be offered for the

behavior of these cases: (1) There may be another source of progestin besides corpus luteum and placenta; or, (2) progestin may not be so important for the continuance of human pregnancy as has been assumed.

DR. C. FREDERIC FLUHMAN, SAN FRANCISCO, CALIF.—The results Browne and his collaborators have obtained in certain cases of habitual abortion are of especial interest and, as more data of this type are accumulated, it will be possible to treat such patients more effectively. It is important to remember, however, that habitual abortion cannot be explained on an endocrine basis in all instances. At other times other factors, not the least of which are the spermatozoa, are primary considerations.

In his graphs I note that the essayist employs the word "prolan" as referring to gonadotrophic substances found in the urine of both nonpregnant and pregnant women. Since these hormones have different biologic properties and probably come from different sources, it seems to me that the word "prolan" should be abandoned owing to the confusion its usage may bring about.

DR. BROWNE (closing).—I would feel that with regard to the removal of the corpus luteum in the cases cited by Pratt before implantation had occurred that there must have been some other source of progesterone. One hesitates to suggest the adrenal cortex as this source, but it is known that progesterone-like activity has been found in this organ.

In regard to the temporary negative values of Jones and Weil, I would emphasize that a negative pregnandiol does not necessarily mean absence of progesterone from the body. There are other links in the chain between progesterone production and excretion of pregnandiol glucuronate. For example, for excretion to occur there must be conjugation of the pregnandiol with glucuronic acid. If there is definite damage to the liver or possibly the kidney, then this will not take place. So that the fact that pregnandiol is temporarily absent after an operative procedure may not mean that progesterone is not present. It may be due to a temporary deviation of glucuronic acid for conjugation with other substances such as is seen after administration of aspirin or to some other interference with the glucuronic acid conjugating mechanism.

Terminology is always a controversial point. I hope that I did not call the gonadotrophic activity present in the normal menstrual cycle "prolan" because one should not say that since it probably differs in its character from the gonadotrophic activity formed in the chorion. The reason that I use the word prolan is that I started doing so when we began our investigations some years ago. I find that to say "chorionic gonadotrophic substance" a hundred times in a lecture takes rather a long time and so I use "prolan" as one would use any abbreviation, and also because it was after all the original term applied to this type of gonadotrophic activity.

With regard to the spelling of the word pregnandiol, I would prefer to leave out the "e" because this was the name originally given to the substance by Butenandt; but while it was correct in German, the chemists tell us that in English the basic hydrocarbon is called "pregnane" and that its di-hydroxy derivative should therefore be called not pregnandiol but pregnanediol.

A CRITICAL SURVEY OF 1,066 CESAREAN SECTIONS*

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THE status of cesarean section in obstetric practice is a much debated subject. There are on the one hand those who seek to increase the scope of the operation and, on the other, those who would restrict its use. The ultimate solution of the problem depends upon an unbiased evaluation of the results of operation as opposed to the results of more conservative types of treatment. The error in the final solution will diminish with the increase in statistics considered, and it is with this thought in mind that our paper is presented.

The background of any report is of importance in evaluating results. During the eighteen years covered by this survey the Obstetric Department of the Methodist Hospital of Brooklyn has been composed of men devoting their practice to obstetrics and gynecology. These men have been responsible for the work of both private and ward services and have supervised the small number of patients delivered on the courtesy service. The only change in the staff has been the addition of younger men so that the results shown here present the experiences of a single group of obstetricians under essentially the same leadership. For the past fourteen years the Obstetric Department has been housed in a pavilion separate from the other services. Both private and ward work is included in this report and no cesarean section has been excluded for any reason.

In 1927 one of us (H. S. A.) was assigned the task of collecting cesarean data from the Methodist Hospital for the survey of cesarean section in Brooklyn sponsored by the Brooklyn Gynecological Society and subsequently published. Since that time every cesarean section at the Methodist Hospital has been reviewed by the same individual for presentation at the monthly staff conference. The interest thus aroused and the detail obtained have made possible this presentation.

Table I presents the total figures with the incidence of cesarean section and the gross morbidity and mortality statistics. The incidence of operation is admittedly high, although there is a tendency throughout the country to approach or even exceed our cesarean ratio. The ratio for the private service greatly exceeds that of the ward so far as total figures are concerned; but this discrepancy is lessened when primary cesarean sections alone are considered. This means, of course, that more repeat cesarean sections are performed on the private service. This fact does not, however, reflect a policy of permitting the ward

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patient to deliver vaginally after having undergone abdominal delivery, for in this respect both services are treated identically. A factor in the higher incidence of operation on the private service is the number of cases referred to the obstetrician after a previous unfortunate experience. In support of this may be cited the fact that of 401 primary cesarean sections done for bony dystocia, 106 had suffered the loss of at least one normal baby from attempted vaginal delivery.

The gross maternal morbidity rate is just over 50 per cent and the mortality rate is 3.18 per cent. These figures are not unlike those of similar clinics, being neither the lowest reported nor by any means the highest. The total fetal mortality rate of 5.2 per cent, which includes all stillbirths and neonatal deaths from all causes, indicates that cesarean section is no certain guaranty of the survival of the infant.

In Table II the cesarean sections are divided into primary and repeat operations. The ratio of primary to repeat cases is more than two to one. The close similarity of the morbidity and mortality rates is interesting.

In Table III the various types of operations comprising the primary and repeat groups are further analyzed. Several points should be noted in this analysis. The first is the lower maternal mortality rate in the primary low flap operations as compared with the classicals. The second is the absence of maternal mortality in the secondary low flap operations, while the secondary classical operations show approximately the same rate as the primary ones. A third is the increase in

TABLE I. GENERAL DATA

Total deliveries Jan. 1, 1920, to Jan. 1, 1938	27,234
Total cesarean sections Jan. 1, 1920, to Jan. 1, 1938	1,066
Total cesarean ratio	1 in 25.5 (3.9%)
Private cesarean ratio	1 in 18.09 (5.5%)
Ward cesarean ratio	1 in 60.0 (1.6%)
Primary cesarean ratio	1 in 37.2 (2.6%)
Private primary cesarean ratio	1 in 29.04 (3.4%)
Ward primary cesarean ratio	1 in 78.06 (1.04%)
Total morbidity	534 (50.09%)
Total maternal mortality	34 (3.18%)
Total fetal mortality	56 (5.2%)

TABLE II. PRIMARY AND REPEAT CESAREAN SECTION

	NUMBER	MORBIDITY	MORTALITY
Primary cesarean sections	730	377 (51.6%)	23 (3.1%)
Repeat cesarean sections	331	152 (45.9%)	11 (3.3%)
Not classified	5	5	0

TABLE III. TYPES OF OPERATION PERFORMED

TYPE OF OPERATION	NUMBER	MORBIDITY	MORTALITY
Primary classical	484	236 (48.7%)	18 (3.7%)
Primary low classical	28	20 (71.4%)	0
Primary low flap	206	112 (54.2%)	5 (2.4%)
Porro	10	7 (70%)	0
Latzko	1	1 (100%)	0
Vaginal cesarean section	1	1 (100%)	0
Secondary classical	206	75 (36.4%)	8 (3.8%)
Secondary low classical	19	11 (57.8%)	0
Secondary low flap	54	39 (72.2%)	0
Tertiary classical	44	22 (50%)	2 (4.5%)
Tertiary low flap	4	4 (100%)	0
Quartan classical	3	0	0

the mortality rate of the tertiary classical operation and the fourth point of interest is the lack of coordination between maternal morbidity and mortality rates. Where the morbidity rate is low the mortality rate may be high and vice versa. This would indicate that determination of morbidity by temperature readings alone is not completely accurate. Our own standard of morbidity is the usual one of a temperature of 100.4° F. or above on two or more successive days up to the twelfth day but excluding the twenty-four hours immediately post partum.

It has been convenient to subdivide the cases in this series into three periods of six years each. The first period (1920-1925) was before the transfer of the service to its separate pavilion, thus segregating the obstetric department. The second period (1926-1931) was marked by the introduction of the intravaginal use of mercurochrome and the low double flap operation. The last period (1932-1937) witnessed a wider application of the low flap operation and more extensive use of the mercurochrome technique. In Table IV is presented the evolutionary trend over these three periods of the types of operation done. The increase in low classical and low flap operations and the decrease in the high classical operation are in accord with experience throughout the country. Here again in the total figures and in those of the last period there is noted the discrepancy between morbidity and mortality figures. The decidedly lower mortality rate of the low flap operation is clearly shown in the total figures. It is noteworthy that in the last six-year period there was an increase in mortality rate of the classical operation over the previous period, but a decrease in the mortality rate of the low flap operation.

TABLE IV. RELATIONSHIP OF THE THREE SIX-YEAR PERIODS

TYPE OF CESAREAN SECTION	1920-1925	1926-1931	1932-1937	TOTAL
Classical No.	291	297	155	743
Morbidity	132 (45.3%)	112 (37.7%)	95 (61.2%)	339 (45.6%)
Mortality	15 (5.1%)	6 (2.02%)	8 (5.1%)	29 (3.9%)
Low classical No.	1	5	41	47
Morbidity	1 (100%)	3 (60%)	27 (65.8%)	31 (65.9%)
Mortality	0	0	0	0
Low flap No.	1	94	169	264
Morbidity	1 (100%)	34 (36.1%)	121 (71.6%)	156 (59.09%)
Mortality	0	2 (2.1%)	3 (1.7%)	5 (1.9%)

TABLE V. INDICATIONS FOR PRIMARY CESAREAN SECTIONS

INDICATION	TOTAL NO.	1920-1925	1926-1931	1932-1937
Contracted pelvis	401	124	157	120
Pre-eclamptic toxemia and nephritis	74	20	33	21
Uterine inertia and cervical dystocia	67	28	22	17
Placenta previa	35	9	13	13
Previous gynecologic operations	27	10	10	7
Pelvic tumors	23	9	6	8
Cardiac	21	2	8	11
Other medical or surgical complications	15	4	3	8
Malpresentation of fetus	13	0	1	12
Eclampsia	12	4	6	2
Premature separation of placenta	9	5	3	1
Elderly primiparas	6	0	1	5
Congenital malformation of vagina or uterus	5	1	3	1
Pendulous abdomen	2	1	1	0
Miscellaneous	20	3	8	9

The most important aspect of the primary cesarean section is the indication therefor. This is of particular interest because this indication not only subjects the patient to the first operation, but in most instances determines the procedure in subsequent pregnancies. Table V lists the various indications for primary cesarean sections and subdivides the cases into the three six-year periods, thus giving opportunity for comparison regarding the continued application of any indication. Contracted pelvis accounts for about 55 per cent of the cases, and this proportion is maintained throughout the three periods. In most surveys pre-eclampsia and nephritis occupy the second place in listing indications. Our series is no exception. Here again the proportion remains about the same over the three periods. Uterine inertia and cervical dystocia, previous gynecologic operations, eclampsia, and accidental hemorrhage have decreased over the years in frequency as indications for cesarean section. However, such indications as placenta previa, cardiac, other medical and surgical complications, malpresentations of the fetus, and elderly primiparas have supplanted them. The increase in operations done for certain malpresentations is particularly striking and is due to earlier recognition of the condition, frequently by means of x-ray, at a time when operation is safer.

Further inquiry into the results of cesarean section done for a specific indication or accompanied by complications reveals certain facts. Table VI is an analysis of the primary cesarean sections operated because of contracted pelvis. The classical operation would seem at first glance to offer greater safety. The causes of death, however, give rise to some concern about this operation. Three of the four deaths following the classical operation were from sepsis. None of the deaths following the low flap operation were from this cause. When we consider that the low flap operation was done after an average of six hours' longer labor and more frequently after rupture of the membranes, it will be seen that this operation was subjected to a severer test than was the classical. Another point of considerable interest is the definitely lower mortality for this group than for the series as a whole.

Table VII presents not only the patients operated primarily for pre-eclampsia and nephritis but also those in whom these complications were a definite factor, despite the listing of another condition as the most potent indication. In these cases the maternal mortality was over twice that of the series as a whole. And while patients exhibiting severe tonic symptoms do show a higher mortality under

TABLE VI. PRIMARY CESAREAN SECTIONS FOR CONTRACTED PELVIS

	NUMBER	MORBIDITY	MORTALITY
Total	401	203 (50.6%)	8 (1.99%)
Classical cesarean sections	253	117 (46%)	4 (1.5%)
Low classical cesarean sections	10	7 (70%)	0
Low flap cesarean sections	138	79 (57.2%)	4 (2.9%)
Classical deaths: Sepsis 3; pneumonia 1			
Low flap deaths: Cardiac 1; pneumonia 1; intestinal obstruction 1; paralytic ileus 1			

TABLE VII. PRIMARY CESAREAN SECTIONS FOR PRE-ECLAMPTIC TOXEMIA AND NEPHRITIS

	NUMBER	MORBIDITY	MORTALITY
Total	74	36 (48.6%)	5 (6.7%)
Classical cesarean sections	58	24 (41.3%)	5 (8.6%)
Low classical cesarean sections	7	5 (71.4%)	0
Low flap cesarean sections	9	7 (77.7%)	0
Classical deaths: Sepsis 2; hemorrhage 1; acute hepatitis 1; cardiac 1			
Other cesarean sections where toxemia was a definite factor			
Classical cesarean sections	19	11	1
Classical death—volvulus			

any conditions, and despite the fact that the cases here presented were those exhibiting the most severe signs and symptoms, the high mortality rate of cesarean section in the toxemias of pregnancy requires serious consideration.

Eclampsia presents a problem even more important than the one just considered. Table VIII presents our experiences with this complication. As was shown in Table VI, we have markedly reduced the number of patients operated upon because of eclampsia. The maternal mortality is too high and all the mortality in our eclamptic patients was referable to the cardiovascular system.

Primary cesarean section because of uterine inertia and cervical dystocia shows a higher maternal mortality rate (Table IX) and higher maternal morbidity rate than the series as a whole. These patients were necessarily subjected to the longest labors and were more frequently subjected to ruptured membranes than any other group. The causes of mortality are of interest. One death was from sepsis. The other two deaths were from pulmonary embolus, the only fatalities following primary cesarean section from this cause. The results of the low flap operation were appreciably better in this group than were those of the high classical operation.

Cesarean section, in the last few years, has come to play a more important role in the management of placenta previa. Those patients who were operated upon primarily for placenta previa (Table X) showed a morbidity higher than average but no maternal mortality. Two factors have contributed largely to this lack of maternal mortality; first, elective operation—none of these patients had ruptured membranes or were subjected to any labor; second, the free use of transfusions. All these patients are typed on admission and there is no hesitation in giving frequent large transfusions, before, during, or after operation.

The mortality rate in patients who were subjected to cesarean section because of previous gynecologic operations (Table XI) is very high, comparable to the

TABLE VIII. PRIMARY CESAREAN SECTIONS FOR ECLAMPSIA

	NUMBER	MORBIDITY	MORTALITY
Total	12	9 (75%)	2 (16.6%)
Classical cesarean sections	9	8 (88.8%)	2 (22.2%)
Low classical cesarean sections	1	1 (100%)	0
Low flap cesarean sections	2	0	0
Classical deaths: Cardiac 1; cerebral embolus 1			
Secondary cesarean sections where eclampsia was a definite factor			
Classical cesarean sections	1	1	1
Classical death—cardiac			

TABLE IX. PRIMARY CESAREAN SECTIONS FOR UTERINE INERTIA AND CERVICAL DYSTOCIA

	NUMBER	MORBIDITY	MORTALITY
Total	67	39 (57.9%)	3 (4.4%)
Classical cesarean sections	37	20 (54%)	2 (5.4%)
Low classical cesarean sections	2	2 (100%)	0
Low flap cesarean sections	28	17 (60.7%)	1 (3.5%)
Classical deaths: Sepsis 1; pulmonary embolus 1			
Low flap death: Pulmonary embolus 1			

TABLE X. PRIMARY CESAREAN SECTIONS DONE FOR PLACENTA PREVIA

	NUMBER	MORBIDITY	MORTALITY
Total	35	21 (60%)	0
Classical cesarean sections	33	19 (57.5%)	0
Low classical cesarean sections	1	1 (100%)	0
Low flap cesarean sections	1	1 (100%)	0

TABLE XI. PRIMARY CESAREAN SECTIONS DONE FOR PREVIOUS GYNECOLOGIC OPERATIONS

	NUMBER	MORBIDITY	MORTALITY
Total	27	13 (48.1%)	2 (7.4%)
Classical cesarean sections	19	9 (47.3%)	2 (10.5%)
Low classical cesarean sections	2	1 (50%)	0
Low flap cesarean sections	6	3 (50%)	0
Classical deaths: Sepsis	2		

rate in the toxemia group. Many of these patients were subjected to labor before cesarean section was deemed necessary. The high mortality suggests either that sterilization should have been done at the time of the gynecologic operation or that cesarean section should have been performed earlier in labor. The two fatal cases had been subjected to prolonged labor. The operative time was not prolonged in either instance. Both deaths were due to sepsis.

The primary cesarean sections performed because of pelvic tumors showed no maternal mortality (Table XII). None of these patients was subjected to more than a very short labor and the majority were done as elective operations. This group was comparable to the placenta previa group in its satisfactory result.

Those patients (Table XIII) who had cesarean section primarily for cardiac disease showed a slightly higher morbidity and mortality rate than the average of the series as a whole. When it is considered that these patients represented the least favorable cases, the mortality rate, one death from cardiac failure, is most encouraging. The number of patients operated upon for this condition shows an increase and the results justify a continuation of the use of cesarean section in properly selected cases.

As regards the other medical and surgical complications, diabetes, acute appendicitis at or near term, intra-partum intestinal obstruction, etc. (Table XIV), the mortality rate in this small series of 15 cases has been excellent. This should not, however, encourage too widespread use of cesarean section for these indica-

TABLE XII. PRIMARY CESAREAN SECTIONS DONE FOR PELVIC TUMORS

	NUMBER	MORBIDITY	MORTALITY
Total	23	12 (52.1%)	0
Classical cesarean sections	18	10 (55.5%)	0
Low classical cesarean sections	1	0	0
Low flap cesarean sections	4	2 (50%)	0

TABLE XIII. PRIMARY CESAREAN SECTIONS DONE FOR CARDIAC DISEASE

	NUMBER	MORBIDITY	MORTALITY
Total	21	11 (52.3%)	1 (4.7%)
Classical cesarean sections	18	10 (55.5%)	1 (5.5%)
Low classical cesarean sections	2	1 (50%)	0
Low flap cesarean sections	1	0	0
Classical death: Cardiac	1		

TABLE XIV. PRIMARY CESAREAN SECTIONS DONE FOR OTHER MEDICAL OR SURGICAL COMPLICATIONS

	NUMBER	MORBIDITY	MORTALITY
Total	15	9 (60%)	0
Classical cesarean sections	13	7 (53.8%)	0
Low classical cesarean sections	0	0	0
Low flap cesarean sections	2	2 (100%)	0

tions, for individual circumstances require the closest scrutiny and cooperation with the medical or surgical consultant.

The group of patients operated upon because of malpresentation of the fetus (Table XV) is small. The cause of death in the one fatal case occurring in this group bears no relation to the indication for operation, but does reflect upon the type of operation done and the length of time consumed in its performance. Most of these patients were operated upon either electively or after a very short test of labor. The one death occurred after an elective operation. Individual factors and supplementary indications, such as slight pelvic contraction, parity, and size of the baby, must play a considerable part in the determination to subject the patient to cesarean section for fetal malpresentation. Another instance of the necessity for individualization.

Premature separation of the placenta (Table XVI) as an indication for cesarean section has not exhibited the excellent fetal results that might be expected, 7 of the babies having died at or shortly after birth. The maternal results, in the small number of cases presented, were excellent, but these same maternal results can be obtained by vaginal delivery. It will be recalled from Table V that this indication has shown a decrease in frequency over the years.

Those elderly primiparas (Table XVII) who were subjected to cesarean section because of their age showed excellent results. These cases were elective and in all the membranes were intact.

The few cesarean sections performed (Table XVIII) for congenital malformation of vagina or uterus are comparable to those done for age of the primipara. These were elective operations and the results were entirely satisfactory.

The results of the repeat cesarean sections (Table XIX) show a higher mortality but a lower morbidity than the series as a whole. All of the deaths in this group followed repetition of the high classical operation. Consideration of the

TABLE XV. PRIMARY CESAREAN SECTIONS FOR MALPRESENTATION OF FETUS

	NUMBER	MORBIDITY	MORTALITY
Total	13	12 (92.3%)	1 (7.6%)
Classical cesarean sections	5	5 (100%)	1 (20%)
Low classical cesarean sections	0	0	0
Low flap cesarean sections	8	7 (87.5%)	0

Classical death: Intestinal obstruction

TABLE XVI. PRIMARY CESAREAN SECTIONS FOR PREMATURE SEPARATION OF THE PLACENTA

	NUMBER	MORBIDITY	MORTALITY
Total	9	4 (44.4%)	0
Classical cesarean sections	8	3 (37.5%)	0
Low classical cesarean sections	1	1 (100%)	0
Low flap cesarean sections	0	0	0
Others where accidental hemorrhage was found			
Classical cesarean sections	5	2	1

Classical death: Hemorrhage

TABLE XVII. PRIMARY CESAREAN SECTIONS FOR "ELDERLY PRIMIPARAS" (35 Yr. or over)

	NUMBER	MORBIDITY	MORTALITY
Total	6	1 (16.6%)	0
Classical cesarean sections	0	0	0
Low classical cesarean sections	1	0	0
Low flap cesarean sections	5	1 (20%)	0

TABLE XVIII. PRIMARY CESAREAN SECTIONS FOR CONGENITAL MALFORMATIONS OF VAGINA OR UTERUS

	NUMBER	MORBIDITY	MORTALITY
Total	5	3 (60%)	0
Classical cesarean sections	3	2 (66.6%)	0
Low classical cesarean sections	0	0	0
Low flap cesarean sections	2	1 (50%)	0

TABLE XIX. REPEAT CESAREAN SECTIONS

	NUMBER	MORBIDITY	MORTALITY
Total	331	152 (45.9%)	11 (3.3%)
Classical cesarean sections	254	98 (34.3%)	11 (4.3%)
Low classical cesarean sections	19	11 (57.8%)	0
Low flap cesarean sections	58	43 (74.1%)	0
All classical: Cardiac 2, pulmonary embolus 2, hemorrhage 1, sepsis 1, intestinal paresis 2, intestinal obstruction 3			

causes of death is of considerable interest. Five of the 11 deaths were attributed to intestinal obstruction, the result of either paresis or adhesions. This high frequency of fatal intestinal complications is in line with our impression of a higher incidence of serious intra-abdominal adhesions following the high classical technique. The low flap operation, as is well known, is not so frequently followed by these complications. While the number of repeat low flap operations is not comparable to that of the high classicals the difference in mortality rates is so striking as to cause comment. The lower incidence of adhesions following the low flap technique is a factor in this difference. Two deaths in this group occurred in patients who suffered a rupture of the previous scar. Since there is less danger of rupture of the low flap scar these two deaths might have been avoided had the previous operation been by the low flap rather than the high classical technique. Pulmonary embolus was the actual cause of death in these two cases. The results of the repeat cesarean sections furnish considerable evidence of the superiority of the low flap technique.

It should be noted in considering the causes of death listed here that sepsis appears as the cause of death in only one repeat cesarean section. In contrast to this may be cited the fact that in 484 primary high classical operations fatal sepsis occurred eight times. This may, at least in part, be accounted for by the fact that elective operations were routinely performed in the repeat group.

A study of the relationship of labor to maternal morbidity and mortality affects chiefly the primary cesarean sections, for it is our routine practice to deliver by prompt elective cesarean section, any patient who has been previously subjected to this operation. Table XX is a comparative study of the results of labor with reference to the high classical and low flap techniques. Unless causes of death are considered in this connection the bare figures are difficult to interpret. The higher mortality in the elective group of classical cases as compared with those subjected to labor of one to twelve hours' duration must be supplemented by this list of causes of death. It will be noted that sepsis occurs twice in the eight deaths of the elective group and three times in the four cases of the group subjected to moderate labor. Further, it will be noted that several of the deaths in the elective group relate to the indication for operation rather than to the operation itself, i.e., the cardiac death was in a patient operated upon because of cardiac disease, the acute hepatitis and cerebral embolus in patients operated upon because of toxemia of pregnancy. It is also interesting that of the fatal cases in the elective group only one patient had ruptured membranes; this was one of the deaths from sepsis. In the group subjected to moderate labor, 3 of the 4 patients had ruptured membranes.

Of the two groups subjected to labor of over twelve hours' duration, the mortality rates are identical. Sepsis, however, appears as the cause of four

deaths in those operated upon by the classical technique; it does not appear as a cause of death after the low flap technique. Of the fatal cases in the classical group 2 had ruptured membranes, 4 unruptured; in the low flap group 1 had ruptured membranes, 4 unruptured. A definite factor in the low flap group is the length of operating time. Three of these 5 cases were subjected to unusually long operations; in each instance the patient was quite obese and the low flap technique was more time consuming. In other words, the deaths in the low flap group, after more than twelve hours of labor, might be more properly assigned to the operator and those of the classical group to the operation.

In Table XXI is presented the relationship of the condition of the membranes to maternal mortality and morbidity. In this connection both primary and repeat cesarean sections are considered. There are included for study here only those cases in which the condition of the membranes was definitely stated. A point of considerable interest is the fact that those patients having ruptured membranes exhibited a lower total maternal mortality than those with membranes intact. The list of causes of death, however, brings out the true status here. It will be noted that of the 586 patients with intact membranes there were 4 deaths from sepsis. Of the 265 patients with ruptured membranes, there were 5 deaths from sepsis. This means that with ruptured membranes the mortality from sepsis is more than twice as great. It must be remembered that the patients with unruptured membranes include many patients whose general condition was disturbed by such conditions as toxemia of pregnancy, heart disease, etc., while those patients with ruptured membranes, particularly those with membranes ruptured

TABLE XX. MATERNAL MORBIDITY AND MORTALITY IN RELATION TO LABOR

	NUMBER	MORBIDITY	MORTALITY
Primary classical (no labor)	208	99 (47.6%)	8 (3.8%) ¹
Primary low flap (no labor)	50	24 (48%)	0
Primary classical (under 12 hr.)	142	63 (44.3%)	4 (2.1%) ²
Primary low flap (under 12 hr.)	43	22 (51.1%)	0
Primary classical (over 12 hr., av. 25.9 hr.)	134	74 (55.2%)	6 (4.4%) ³
Primary low flap (over 12 hr., av. 31.1 hr.)	113	66 (58.3%)	5 (4.4%) ⁴

¹Causes of death: Sepsis 2, cardiac 2, hemorrhage 1, cerebral embolus 1, acute hepatitis 1, intestinal 1.

²Causes of death: Sepsis 3, pneumonia 1.

³Causes of death: Sepsis 4, cardiac 1, pulmonary embolus 1.

⁴Causes of death: Intestinal 2, pneumonia 1, cardiac dilatation 1, pulmonary embolus 1.

TABLE XXI. CONDITION OF MEMBRANES IN RELATION TO MORBIDITY AND MORTALITY

	NUMBER	MORBIDITY	MORTALITY
Membranes intact	586	272 (46.4%)	21 (3.5%) ¹
Membranes ruptured	265	151 (56.9%)	9 (3.4%) ²
Time undetermined	37	25	2 ³
Up to 12 hours	138	73 (52.9%)	4 (2.9%) ⁴
12 to 24 hours	49	25 (51.0%)	2 (4.08%) ⁵
Over 24 hours	41	28 (68.2%)	1 (2.4%) ⁶

¹Causes of death: Intestinal 8, sepsis 4, pulmonary embolus 2, hemorrhage 2, cardiac 2, pneumonia 1, acute hepatitis 1, cerebral embolus 1.

²Causes of death: Sepsis 5, cardiac 2, pneumonia 1, pulmonary embolus 1.

³Causes of death: Sepsis 2.

⁴Causes of death: Sepsis 1, cardiac 1, pneumonia 1, pulmonary embolus 1.

⁵Causes of death: Sepsis 2.

⁶Cause of death: Cardiac 1.

over twelve hours, include the patients in good general condition; the indication for whose operation was contracted pelvis. And it must be remembered that the patients operated upon because of contracted pelvis exhibited the lowest maternal mortality. The fact that no sepsis deaths occurred in the group with membranes ruptured over twenty-four hours may be explained by the greater use of the low flap technique in these cases.

A comparative study of the effects of ruptured membranes on the outcome after use of the high classical and low flap techniques is made in Table XXII. The mortality rate for the low flap is higher in those patients with membranes intact, but the low flap mortality includes no case of sepsis; the classical list includes four such deaths. Where there has been rupture of the membranes, one-half of the deaths after classical cesarean section are from sepsis, and the mortality rate from the classical operation far exceeds that of the low flap. The classical cesarean section is much more likely to be followed by fatal sepsis when the barrier of intact membranes has been removed.

Anesthesia (Table XXIII) is of importance in considering cesarean sections. General anesthesia, consisting of gas, oxygen, and ether, was by far the most frequently used. Twenty-one respiratory infections followed the use of general anesthesia. Included in these was one fatal case of pneumonia. In our clinic the results from general anesthesia have been very satisfactory because of its administration by a staff of properly trained nurses.

Spinal anesthesia was used in 90 cases with no maternal mortality and with a lower morbidity than the average of the series. Twenty-six of these cases were toxic patients and the results in them were excellent. Three respiratory infections were encountered following this type of anesthesia. These patients had respiratory infections before operation. Spinal anesthesia has not been established as a routine in our service but has been used only on indication. Upper respiratory infections and toxemia are the most frequent such indications. When properly indicated and when given by those experienced in its use spinal anesthesia has a definite place in cesarean section and many clinics would do well to use it more frequently.

TABLE XXII. COMPARISON OF LOW FLAP AND CLASSICAL AS TO CONDITION OF MEMBRANES

	NUMBER	MORBIDITY	MORTALITY
Membranes intact			
Classical	469	194 (41.3%)	17 (3.6%) ¹
Low flap	84	54 (64.2%)	4 (4.7%) ²
Membranes ruptured up to 12 hr.			
Classical	92	44 (47.8%)	4 (4.3%) ³
Low flap	39	25 (64.1%)	0
Membranes ruptured over 12 hr.			
Classical	42	25 (59.5%)	2 (4.7%) ⁴
Low flap	47	27 (57.4%)	1 (2.1%) ⁵

¹Causes of death: Intestinal 6, sepsis 4, pulmonary embolus 1, hemorrhage 2, cardiac 2, acute hepatitis 1, cerebral embolus 1.

²Causes of death: Intestinal 2, pneumonia 1, pulmonary embolus 1.

³Causes of death: Sepsis 1, cardiac 1, pneumonia 1, pulmonary embolus 1.

⁴Causes of death: Sepsis 2.

⁵Cause of death: Cardiac 1.

TABLE XXIII. ANESTHESIA

TYPE	NUMBER	MORBIDITY	MORTALITY
Avertin	5	4 (80.0%)	0
Local	38	22 (57.8%)	4 (10.5%)
Spinal	90	44 (48.8%)	0
General	933	464 (49.7%)	30 (3.2%)

Our experience with both local anesthesia and avertin has been very limited and the small number of cases does not permit intelligent comment. Local anesthesia is coming to assume more importance, and its use is being successfully extended in our clinic. Three of the four deaths listed here under local anesthesia were due to intestinal obstruction following repeat classical operations. The fourth death was from pneumonia, local anesthesia having been used because of severe upper respiratory infection.

Table XXIV presents the causes of morbidity according to the type of cesarean section performed. The unexplained morbidities include those where "reaction" was given as the cause. All these morbidities were of short duration, two to three days, and did not cause any prolongation of hospital stay. The group that would be considered as sepsis, i.e., pelvic thrombophlebitis, pelvic peritonitis, bacteriemia, peritonitis and puerperal sepsis, was much more prevalent after classical than after low flap operations. The milder grades of infection, including sapremic infections, were more nearly equally divided between the two types of operations, since the ratio of classical to low flap operations was approximately three to one. This relationship also holds for the number of infected wounds. There were two instances, both following low flap operations, in which there was complete rupture of the wound. Both these occurred in patients who had severe pulmonary infections, pneumonia and bronchitis, but both survived.

TABLE XXIV. CAUSES OF MORBIDITY

	CLASSICAL	LOW CLASSICAL	LOW FLAP
Unexplained (includes "reaction" temperatures)	180	17	104
Infected wound	42	3	12
Peritonitis	4	0	0
Pelvic infection	6	1	2
Puerperal sepsis	4	0	0
Pelvic thrombophlebitis	2	0	0
Bacteriemia	2	0	0
Respiratory infections	23	2	11
Sapremia (lochia metra)	33	4	12
Pyelitis	12	1	9
Phlebitis	12	1	3
Hemorrhage	5	0	0
Breast infections	3	1	0
Eclampsia	3	0	0
Paralytic ileus	2	0	2
Parotitis	2	0	1
Axillary abscess	2	0	0
Abscess of uterine wall	2	0	0
Acute colitis	0	1	0
Acute cholecystitis	0	0	1

Post-partum hemorrhage was considered the cause of morbidity in 5 cases. This complication occurred in a total of 9 cases in the series and in 2 instances was the cause of death. The majority of these cases occurred after the high classical operation and both fatal cases were included in these. One hemorrhage followed the successful use of local anesthesia, 1 followed spinal and 7 followed general anesthesia.

One other complication, while not listed as a cause of morbidity, deserves mention. There were 8 patients in whom rupture of the previous cesarean scar occurred. Four of these patients had had 2 previous high classical cesarean sections, 3 had had 1 previous high classical operation, and 1 patient had had a previous low flap operation. Two deaths occurred in the 8 cases, both in patients who had had two previous high classical operations. The cause of death in each instance was pulmonary embolus. In 3 instances the rupture caused no symptoms and was found at routine repeat operation before the onset of labor.

In Table XXV is a recapitulation of the most important consideration in cesarean section, maternal deaths. There were 34 fatalities in our series, and the various causes are listed. The high classical technique is credited with 29 of these deaths, the low flap with 5. We have discussed most of these cases from the point of view of indication for operation, but certain factors should be stressed. No deaths from sepsis occurred following the low flap technique. The greatest number of deaths from intestinal complications occurred after repetition of the high classical technique. The cardiovascular deaths occurred, in one patient operated upon because of cardiac disease, and in 4 patients operated upon because of toxemia or eclampsia; in the other 2 cases death was attributed to acute cardiac dilatation although shock may have been the underlying cause. The deaths from pulmonary embolus were equally divided between the patients with rupture of the previous scar and those patients operated upon because of uterine inertia and cervical dystocia. Only 2 patients died of pneumonia and 2 of hemorrhage. One patient died of acute fulminating hepatitis. Our present knowledge presents no solution to this problem.

TABLE XXV. MATERNAL DEATHS

	CLASSICAL		LOW FLAP		TOTAL
	PRIMARY	REPEAT	PRIMARY	REPEAT	
Sepsis	8	1	0	0	9
Intestinal obstruction (Including paresis)	2	5	2	0	9
Cardiovascular	4	2	1	0	7
Pulmonary embolus	1	2	1	0	4
Pneumonia	1	0	1	0	2
Hemorrhage	1	1	0	0	2
Acute hepatitis	1	0	0	0	1

No deaths followed low classical operations

SUMMARY

In the face of bare figures, the high classical technique stands convicted of a high maternal mortality, 3.9 per cent for all the classical operations as against 1.8 per cent for all the low flap operations. It has been shown, however, in this analysis that type of operation alone cannot be condemned. The classical technique bore the brunt of responsibility for such indications as toxemia and nephritis and cardiac and pulmonary diseases where the patient did not enter the operating room in good general physical condition, and where speed of operation was a most important consideration. There was one instance, however, where the high classical operation did fail badly, namely in the prevention of sepsis. The low flap technique has in this series been responsible for no fatality from sepsis. As was shown in the discussion on labor the fatal cases following the low flap technique were attributable more to the technique of the operator than to the technique of the operation. The factor of experience of the obstetrician is one that cannot be overlooked. In listing the fatal cases in chronologic order and including the name of the operator, in preparing this study, it was an outstanding fact that the younger men of the service were much more frequently associated with maternal mortality. As time progressed and these men became more experienced their names did not nearly so frequently appear in this listing. This fact is noteworthy, for it occurred in spite of the organization of our service

which demands and provides for careful supervision of younger men by those of greater experience. This factor of personal experience must receive due consideration in evaluating any group of figures.

In concluding this survey, stress must be laid upon certain points. The maternal mortality of cesarean section is high, too high following some indications, particularly the toxemias of pregnancy. These weak spots must either be eradicated or bolstered by a change in technique. Because of its greater incidence of sepsis and poorer results in repeat operations, the classical operation should be reserved for those cases where the element of time is of prime importance. The low flap operation is slightly more difficult in its performance, particularly in the obese patient, and the mortality associated with it can be more frequently attributed to the operator than to the operation. If cesarean section is to take its proper place as a means of escaping obstetric difficulties, the following postulates must be rigidly observed: There must be a correct indication for operation. The proper type of operation must be performed at the proper time. The operation must be performed by an obstetrician with surgical experience.

643 ST. MARKS AVENUE
632 SECOND STREET

BACTERIOLOGY OF THE UTERUS AT CESAREAN SECTION*

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AN ANALYSIS of 144 uterine cultures taken at cesarean section is presented in order to demonstrate the apparent value of antiseptic vaginal instillations in the preparation of the patient for operation. Cultures were obtained from 52 per cent of the patients operated upon during a period of eight years at the St. Louis Maternity Hospital. The causes of mortality were determined and the elimination of infection as an important factor will be noted. A very practical finding is that when a case has received the benefit of antiseptic vaginal instillations before operation the time of operation may be safely postponed much longer than has been formerly recommended.

The report of Harris and J. H. Brown,¹ in 1927, suggested the idea and method of culturing the uterus at cesarean section. They stated "the excessive maternal mortality is due in great part at least, to the fact that it is not generally recognized that the danger of the operation increases progressively with every hour elapsing after the onset of labor, and is explained by finding that an ascending infection of the uterus occurs whenever labor has progressed for some time. Williams,² in 1917, first adduced histologic evidence concerning the occurrence of such infections, which was still further confirmed when one of us (J. W. H.³) demonstrated its existence in 22 of 33 uteri removed by supravaginal hysterectomy following cesarean section when labor had lasted six or more hours.

"Walther,⁴ in 1919, reported that positive cultures were obtained from the amniotic fluid and uterine secretion at 15 cesarean sections. He failed to state how long the patients had been in labor when the operation was done, but most of them had been in the hands of midwives or physicians before admission to the clinic, and in all of them five to eighty hours had elapsed between the rupture of the membranes and the time of operation."

The same method of obtaining the culture was used in the present study as described by Harris and J. H. Brown.¹ "All of the cultures were taken through the uterine incision, in order to insure that they could not be contaminated by the vaginal secretion. As soon as the child was delivered, and before the hands or the instruments had been introduced into the lower uterine segment, a sterile, cotton-covered swab was passed through the uterine incision and rubbed over the lower uterine segment, care being taken that it did not come in contact with any portion of the uterus except that from which the culture was desired." The cultures should be inoculated as soon as possible and smears made and stained with Gram's stain. Three tube cultures are made routinely: an aerobic blood agar slant, a cooked meat tube, and an anaerobic blood agar slant using Wright's⁵ technique. This method has been found to be practical and satisfactory in the search for anaerobic organisms.

*Read, by invitation, at the Sixty-fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

The same classification of operations is used in this report. Nevertheless the radical procedure (supravaginal hysterectomy) was not performed because of infection, but for the purpose of sterilization or removal of a myomatous uterus.

Harris and J. H. Brown¹ found positive uterine cultures in 44 per cent of their series of 50 cases. They noted the predominance of anaerobic streptococci. Anaerobic growth was obtained in 45 per cent of the positive cultures. "No sterile cultures were obtained from patients in whom active labor had lasted for six hours or more and only one positive culture was obtained where labor had progressed less than six hours." "... when cesarean section is definitely indicated the ideal time for its performance is at an appointed time at the end of pregnancy or at the very beginning of labor." Later in labor they suggest employment of the low cervical section or the radical procedure (supravaginal hysterectomy). Antiseptic treatment of the vagina preparatory to operation was not mentioned in their paper.

Douglas and Rhees⁶ studied cultures of the uterus in a series of 20 cesarean sections and obtained positive cultures on 7, or 30 per cent. Six of these patients had been in labor for an average of 27.9 hours. Anaerobic streptococci were most frequently found. No vaginal preparation was mentioned in this group of cases. "All patients on whom cesarean section was performed and who showed positive uterine cultures at the time of operation, later developed febrile puerperia."

Dieckmann⁷ stressed the importance of infection as the main cause of mortality in 945 cesarean sections, 50 per cent.

DISCUSSION

The use of vaginal instillations during labor was instituted on our service by Dr. W. J. Dieckmann (1926). At first they consisted of a 3 per cent mercurochrome and 0.03 per cent iodine solution in glycerin. This resulted in a definite improvement in morbidity and mortality. On Jan. 1, 1931, at the suggestion of Dr. E. A. Graham, the type of instillation used was changed to 1 per cent neutral acriflavine in glycerin. This was done because of the rather specific affinity of acriflavine for cocci. The chief offenders in our study had been shown to be anaerobic streptococci. Eight cubic centimeters of the solution were instilled into the vagina upon admission of the patient and before subsequent examinations. Later this treatment of the vagina was carried out every six hours during labor, and for several years has been ordered every four hours. In numerous cases the degree of penetration of this dye substance has been observed to extend four inches above the external os.

To prepare the vagina before a gynecologic procedure and not to do so before cesarean section, appears somewhat inconsistent. In the latter case the peritoneal cavity is exposed to contamination from the vagina, and in the former there may be no such exposure. The type of positive cultures obtained from the uteri at section is similar to those of the vaginal flora, 83 per cent anaerobic. Soule and the author studied the vaginal flora of normal clinic patients during pregnancy and found anaerobic growth in 60 per cent of the cases. The vagina seems to be the most logical source of contamination in cesarean section, and the use of

antiseptic vaginal instillations as a means of prevention of such contamination appears to be most rational.

TABLE I. JOHNS HOPKINS HOSPITAL
(Reported by J. W. Harris and J. H. Brown, 1927)

Total uterine cultures		50	
Analysis			
Negative		28	
Positive		22 (44%)	
(Anaerobic growth		45%)	
Classical sections	31	Low cervical sections	13
Analysis		Analysis	
Negative		Negative	
Positive		Positive	
(Anaerobic growth, 50%)		(Anaerobic growth, 50%)	
Radical sections		6	
Analysis		Analysis	
Negative		Negative	
Positive		Positive	
(Anaerobic growth, 20%)		(Anaerobic growth, 20%)	

The findings of Harris and J. H. Brown¹ on the service at Johns Hopkins Hospital are shown in Table I. Vaginal preparation was not practiced in this series of 50 cases and positive uterine cultures were obtained in 22 cases at the time of section (44 per cent). Anaerobic growth was noted in 45 per cent of the positive cultures, emphasizing again this group of organisms as the chief offenders. Their conclusion was that, "no sterile cultures were obtained from patients in whom active labor had lasted for six hours or more and only one positive culture was obtained where labor had progressed less than six hours." After six hours of labor they suggested the use of the low cervical section or the radical procedure (supravaginal hysterectomy). May we not use these results as a control group to compare with the present series in which vaginal instillations were consistently used as a part of the routine preparation?

TABLE II. ST. LOUIS MATERNITY HOSPITAL
(Jan. 1, 1931 to Jan. 1, 1939)

Total uterine cultures		144	
Analysis			
Negative		138	
Positive		6 (4.1%)	
(Anaerobic growth, 83%)			
Classical sections	47	Low cervical sections	66
Analysis		Analysis	
Negative		Negative	
Positive		Positive	
(1 Intra-partum infection, mixed)		(1 Intra-partum infection)	
Anaerobic growth, 100%		Anaerobic growth, 66%	
Radical sections		31	
Analysis		Analysis	
Negative		Negative	
Positive		Positive	
(Intra-partum infection)		(Intra-partum infection)	
Anaerobic growth, 100%		Anaerobic growth, 100%	

Table II gives the results obtained in a series of 144 uterine cultures on the service of the St. Louis Maternity Hospital. All but 10 of these patients received the aeriflavine instillations routinely. Only 6 positive cultures were found, an incidence of 4.1 per cent. This is but one-tenth the incidence noted in the study from Johns Hopkins Hospital. Anaerobic growth was present in 83 per cent of the positive cultures. A pure aerobic culture was obtained in one instance of a face presentation which had been in labor for forty-eight hours with ruptured membranes for the same length of time. *B. coli* was grown on the culture. There were no complications in this case. Intra-partum infection was present in 3 (50 per cent) of the patients with positive uterine cultures.

TABLE III. ST. LOUIS MATERNITY HOSPITAL. CESAREAN SECTIONS, CLASSICAL

Total cases by this method				47
POSITIVE CULTURES				Negative CULTURES
Receiving acriflavine	Aerob.	Mixed—1	Anaerob.	41
in glycerin		(Intra partum)		
Not receiving	Aerob.	Mixed	Anaerob.—1	4
acriflavine in glycerin				
Elective				42
Afebrile				33
Ruptured membranes				11
Extremes—40 minutes to 56½ hours				
In labor				9
Extremes—2 hours to 74 hours (3 less than 6 hours, 6 more than 6 hours)				
Vaginal examination				15
Excellent healing of wound				41
DeLee shuttle				15
Deaths				0
Temperature: 37.5° C. or more on day of operation				1
Considered afebrile if cause of fever was outside genital tract.				

Table III analyzes the group of classical sections of Table II in more detail. One case with a positive culture was found to be a mixed contamination, with both aerobic and anaerobic organisms. Instillations were not started until late in labor because the patient was not admitted to the hospital until intra-partum infection was present. Another patient showed anaerobic growth and had received no instillations. It was an elective section and the membranes were intact. This seems to lend further support to the idea that intact membranes are permeable to bacteria. In 11 cases the membranes had been ruptured from forty minutes to 56½ hours. Nine patients were in labor, 3 less than six hours and 6 more than six hours. One patient had a temperature of 37.5° C. or more on the day of operation.

TABLE IV. ST. LOUIS MATERNITY HOSPITAL. CESAREAN SECTIONS, LOW CERVICAL

Total cases by this method				66
CULTURES:	Longitudinal		Transverse	
	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE
	Aer.	Mixed	Anaer.	
Receiving acriflavine	17		1	1
in glycerin			(Face)	(Bag)
Not receiving	2			1
acriflavine in glycerin				(Intra partum)
				(1 merthiolate and glycerin)
Elective				39
Afebrile				39
Ruptured membranes				31
Extremes—1½ to 89¾ hours				
In labor				34
Extremes—2¼ to 107½ hours (4 less than 6, 30 more than 6 hours)				
Vaginal examinations				28
Excellent healing of wound				51
DeLee shuttle: Longitudinal, 2; Transverse, 22; Total				24
Deaths				0
Temperature: 37.5° C. or more on day of operation				9
2 cases attempted forceps delivery before section, 1 bag induction.				
Considered afebrile if cause of fever was found outside genital tract.				

Table IV shows 3 positive uterine cultures in the low cervical sections: one aerobic, with *B. coli* present after a labor of forty-eight hours with ruptured mem-

branes and a face presentation; 1 mixed (aerobic and anaerobic) in a patient in labor twenty-four hours with membranes ruptured thirty hours and bag induction attempted; 1 anaerobic intra-partum infection. A negative uterine culture was obtained in an elective section in which an instillation of merthiolate in glycerin was substituted for the acriflavine instillation. The membranes were ruptured in 31 patients from 1½ hours to 89¾ hours. In 34 patients labor had been in progress from 2¼ hours to 107½ hours, 4 less than six hours and 30 more than six hours. In 2 patients forceps delivery was attempted before cesarean section was performed, and in each, the uterine culture was negative. Nine patients had temperatures of 37.5° C. or more on the day of operation.

TABLE V. ST. LOUIS MATERNITY HOSPITAL. CESAREAN SECTIONS, RADICAL

Total cases by this method			31
POSITIVE CULTURES			NEGATIVE CULTURES
Receiving acriflavine in glycerin	Aerob. Mixed Anaer.—1 (Intra partum)		29
Not receiving acriflavine in glycerin	Aerob. Mixed Anaer.		1
Elective			28
Afebrile			21
Ruptured membranes			4
Extremes—10 hours to 2 weeks			
In labor			4
Extremes—1¼ to 79 hours (1 less than 6, 3 more than 6 hours)			
Vaginal examinations			7
Excellent healing of wound			21
Deaths (hemorrhage)			1
Indications for removal of uterus	{Sterilization Myoma	25 6	31
Temperature: 37.5° C. or more on day of operation			1
Considered afebrile if cause of fever was found outside of genital tract.			

Table V has one positive uterine culture in the radical sections. This was anaerobic and in an intra-partum infection. In 4 patients the membranes were ruptured for from ten hours to two weeks before operation. Four patients were in labor from 1¼ hours to 79 hours, 1 less than six hours and 3 more than six hours. One death resulted in this group of cases because of hemorrhage from a pedicle. The indications for removal of the uterus were: sterilization in 25, and myoma in 6. One patient had a temperature of 37.5° C. or more on the day of operation.

TABLE VI. ST. LOUIS MATERNITY HOSPITAL

Total uterine cultures Jan. 1, 1931, to Jan. 1, 1939		144 (52.5%)
Analyses of cultures		
Negative	138	
Positive	6 (1 elective)	
Aerobic (B. coli)	1	
Mixed (1 Intra partum)	2	
Anaerobic growth		83%
Deaths in cases cultured		1
Cause		
Infection	0	
Hemorrhage	1	
		NEGATIVE POSITIVE
134 patients prepared with acriflavine	129 (100 elective)	5 (not elective)
10 patients not prepared with acriflavine	9 (8 elective)	1 (elective-anaerobe)
35 patients were not elective and only 5 of these had positive cultures (14%)		

Table VI reports 144 uterine cultures obtained in 274 sections performed, or 52.5 per cent. Of the 6 positive cultures obtained, 1 was elective and 5 were not. Three cases were intra-partum infections in which the infection was present before the instillations were started. One death occurred among the cases cultured, and it was due to hemorrhage. Nine of the 10 cases not prepared with the instillations were elective sections which would likely not be contaminated, although an anaerobic culture was obtained in one instance. A total of 35 cases were not elective and only 5 of these patients were found to have positive cultures (14 per cent).

TABLE VII. ST. LOUIS MATERNITY HOSPITAL

(Jan. 1, 1931 to Jan. 1, 1939)

Total deliveries	12,579
Total deaths	44 (1—285)
Corrected deaths	35 (1—359)
Total sections	274 (1—45)
Total deaths in section cases	6 (1—2096) (1—45 sections)
Analysis as to cause	
Infection, puerperal	3* (year 1931)
Hemorrhage	1
Toxemia	1
Cardiac	1

*Puerperal infection was accountable for 50 per cent of the deaths and each of these deaths occurred during 1931, when the use of acriflavine instillations was in the experimental stage.

Table VII gives total deliveries, deaths, and sections. No death from puerperal infection has occurred in 12,579 deliveries, except the 3 deaths associated with delivery by cesarean section. The deaths following cesarean section are analyzed, and it is shown that puerperal infection was accountable for 50 per cent of the deaths and each of these 3 deaths occurred during the year 1931, when the use of acriflavine instillations was in the experimental stage. Since 1931, this most important cause of mortality associated with cesarean section seems to have been brought under control. Intra-partum infections may still occur and be the cause of considerable anxiety.

Adair⁹ states that, "Actual genital infection of the parturient woman has been considered a contraindication to any type of cesarean section except in case of the absolute indication when it should be associated with a hysterectomy or Porro operation. The absolute indication for cesarean section exists when it is not possible to deliver either a living or a dead baby through the parturient canal without serious damage or danger to the mother.

"We recognize parturient cases with potential or actual genital infection. In the potential group we place those patients who have been exposed to genital infection by vaginal examination or manipulation during labor, those who have been in labor twenty-four hours or longer, and those in whom the membranes have been ruptured twelve to twenty-four hours or longer. We do not perform any type of cesarean section on these patients if they can be delivered through the natural passages with relative safety to the mother and baby. Where the exposure has been considerable, a Porro hysterectomy may be a necessary sequence to an indicated cesarean section.

"The actually infected patients include those who present clinical and laboratory evidence of an infection with or without localizing genital findings. In the latter group those without findings which locate an infection as extragenital are regarded as having a genital infection. Our opinion is that all actual infection is still a contraindication to cesarean section. The only indication for cesarean section in these cases is the absolute one, i.e., where a dead fetus cannot be delivered even by craniotomy through the parturient canal. When a cesarean section is necessary, we believe a hysterectomy is a necessary sequence.

"... We have records of 20 Porro operations in infected cases. Of these there were 12 potential and 8 actual infections. There were additional indications for hysterectomy in many of these patients. There was no mortality in our series."

In our series 23 patients (15.9 per cent) were in labor twenty-four hours or longer. Culture of the uterus was negative in 18 of these cases (an incidence of 78.2 per cent). Five cases were found to have positive uterine cultures after being in labor for this period of time: three of these were intra-partum infections; 1 had a bag induction; and, 1 was a brow presentation in a myomatous uterus. The mortality was nihil.

The 3 patients who died as the result of puerperal infection occurred early in this study (1931). Culture of the uterus was not obtained in each instance. The first patient received 1 instillation and then had an emergency section for rupture of a previous cesarean scar. Temperature was normal on admission. *Staphylococcus albus* was found on blood culture, wound culture, and later on uterine culture. The second case had normal temperature on admission. An instillation was given once a day for five days before operation. Blood culture showed *Streptococcus hemolyticus*. A previous cesarean section had been done on this patient a year and a half previously with no morbidity. The third case was one of intra-partum infection. Four instillations were given. Two days postoperatively the patient's husband informed us that a midwife had examined the patient several times before admission to the hospital. Peritoneal culture showed a mixed culture (aerobic and anaerobic organisms).

SUMMARY

1. In a report from Johns Hopkins Hospital, 44 per cent positive uterine cultures were found without the use of instillations.
2. In our series, 4.1 per cent positive uterine cultures were obtained with the routine use of acriflavine instillations.
3. The importance of anaerobic organisms as the chief contaminants is stressed.
4. With the use of antiseptic instillations the period of time in labor may be greatly prolonged with negative cultures being obtained as late as 107½ hours after the onset of labor.
5. Intra-partum infection may be present on admission and vaginal instillations are too late to be of real value.
6. Among the patients cultured there was one death which resulted from hemorrhage.
7. Fifty-two and five-tenths per cent of the patients who had cesarean sections were cultured.
8. Of the 6 positive cultures, 5 were not elective cases.
9. Thirty-five cases were not elective and only five of these patients had positive cultures (14 per cent).
10. Positive cultures can be obtained with membranes intact.
11. The morbidity in this series was 52.8 per cent.
12. Three deaths from puerperal infection occurred during the first year of the study.
13. Instillations should be given prophylactically twice daily on waiting cases and every four hours if in labor.

CONCLUSION

Antiseptic vaginal instillations offer a means of preparation of a patient for cesarean section which will (1) largely eliminate one of the most important causes of mortality, infection; (2) reduce the incidence of positive uterine cultures obtained; (3) make it relatively safe to postpone operation until a much later hour in labor; and, (4) lower the indication for the more radical operative procedures. Of course, intra-partum infection may occur and this can only be prevented by the earlier prophylactic use of the instillations.

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DISCUSSION ON THE PAPERS OF DRS. MATTHEWS AND ACKEN,
AND BROWN

DR. FRED L. ADAIR, CHICAGO, ILL.—My report from the service of the Chicago Lying-in hospital covers 500 cesarean sections. Tubal ligation was practiced in about 36 per cent of these cases, most of which were repeat sections.

Table I shows the types of operations and Table II the indications for the sections.

TABLE I. TYPES OF OPERATIONS

	PER CENT
279 Laparotrachelotomies	55.8
183 Laparotrachelotomies and sterilization	36.4
30 Porro cesarean sections	6.0
8 Classical cesarean sections	1.6
(Four sterilized)	

TABLE II. 500 CESAREAN SECTIONS

	CASES	PER CENT
<i>Indications (Major Factor):</i>		
Contracted pelvis	200	40.0
Pre-eclampsia	44	8.8
Placenta previa	40	8.0
Previous cesarean section	39	7.8
Cardiac disease	35	7.0
Abruptio placentae	25	5.0
Dystocia dystrophy syndrome	22	4.4
Chronic nephritis	20	4.0
Cervical dystocia	12	2.4
Cephalopelvic disproportion	10	2.0
Eclampsia	8	1.6
Previous repeated stillbirths	8	1.6
Fibromyoma uteri	5	1.0
Miscellaneous	30	6.0

Cultures were taken on most of these cases in conformity with our routine procedures for all abdominal operations. The main objective of our three culture

techniques was to determine the presence and time of contamination during an abdominal operation. The following method was followed in making our I, II, III cultures (Table III).

TABLE III

Culture I

The first culture was taken after the incision was made down to the peritoneum. Organisms found, after having been cultured, were introduced from any one or more of the following sources: instruments, instrument table, drapes, gloves, operator, operating assistants, abdominal skin after preparation with benzene, ether, iodine, alcohol, etc.

Culture II

The second culture was taken immediately after the peritoneum was nicked. This culture denoted what organisms were present in the peritoneal cavity.

Culture III

The third culture was taken in the operative field immediately before closure of the peritoneum. Organisms usually found are those that were found in both Culture I and Culture II, in addition to any intrauterine, cervical or vaginal organisms.

TABLE IV. CULTURE I

	CASES	PER CENT OF POSITIVE
<i>L. gram + diplococcus</i>	36	24.81
<i>Staph. albus</i>	33	22.75
Gram + diphtheroids	19	13.10
<i>Strep. diplobacillus</i>	12	8.27
Anaerobic strep.	9	6.20
<i>Strep. hemolyticus</i>	8	5.52
Döderlein's bacillus	7	4.55
<i>B. subtilis</i>	5	3.42
<i>B. mesentericus</i>	4	2.76
Gram + rods	3	2.07
<i>B. proteus</i>	2	1.38
Nonhemolytic strep.	2	1.38
Miscellaneous	4	2.76

TABLE V. CULTURE II

	CASES	PER CENT OF POSITIVE
<i>L. gram + diplobacillus</i>	35	25.54
G. + diphtheroids	25	18.24
<i>B. mesentericus</i>	22	16.05
<i>Staph. albus</i>	18	13.13
Anaerobic strep.	7	5.10
<i>Strep. diplobacillus</i>	6	4.43
Döderlein's bacillus	5	3.64
Gram + rods	5	3.64
<i>B. proteus</i>	3	2.18
<i>B. prodigiosus</i>	3	2.18
<i>B. subtilis</i>	3	2.18
<i>Strep. hemolyticus</i>	3	2.18
Miscellaneous	2	1.46

The tables following will show the number and percentage of positive and negative cultures and the organisms which were found in the different series. Table IV shows the percentage of different organisms from Culture I, found in those cases where positive cultures were obtained. Table V shows similar data from Culture II and Table VI shows similar data for Culture III. Table VII shows the percentage of negative cultures obtained in all cases and the percentage of all cases in which various organisms were found by Culture I. Table VIII shows similar data for Culture II and Table IX shows similar data for Culture III.

TABLE VI. CULTURE III

	CASES	PER CENT OF POSITIVE
<i>G. gram + diplobacillus</i>	88	26.99
<i>Staph. albus</i>	75	23.00
Gram + diphtheroids	63	19.35
<i>Strep. diplobacillus</i>	24	7.36
Döderlein's bacillus	17	5.21
Anaerobic strep.	13	3.99
<i>B. subtilis</i>	9	2.76
<i>B. mesentericus</i>	9	2.76
Gram + rods	9	2.76
<i>Strep. hemolyticus</i>	8	2.44
<i>B. coli</i>	4	1.22
<i>Strep. proteus</i>	2	0.61
Miscellaneous	4	1.22

TABLE VII. CULTURE I

	CASES	PER CENT OF ALL
Negative	357	71.11
<i>L. gram + diplobacillus</i>	36	7.11
<i>Staph. albus</i>	33	6.57
Gram + diphtheroids	19	3.78
<i>Strep. diplobacillus</i>	12	2.37
Anaerobic strep.	9	1.79
<i>Strep. hemolyticus</i>	8	1.59
Döderlein's bacillus	7	1.39
<i>B. subtilis</i>	5	1.00
<i>B. mesentericus</i>	4	0.80
Gram + rods	3	0.60
<i>B. proteus</i>	2	0.40
Nonhemolytic strep.	2	0.40
Miscellaneous	4	0.80

TABLE VIII. CULTURE II

	CASES	PER CENT OF ALL
Negative	363	72.60
<i>L. gram + diplobacillus</i>	35	7.00
Gram + diphtheroids	25	5.00
<i>B. mesentericus</i>	22	4.40
<i>Staph. albus</i>	18	3.60
Anaerobic strep.	7	1.40
<i>Strep. diplobacillus</i>	6	1.20
Döderlein's bacillus	5	1.00
Gram + rods	5	1.00
<i>B. proteus</i>	3	0.60
<i>B. prodigiosus</i>	3	0.60
<i>B. subtilis</i>	3	0.60
<i>Strep. hemolyticus</i>	3	0.60
Miscellaneous	2	0.40

I would like to stress that, while we do not use vaginal instillations as a routine procedure, the acriflavine and glycerin mixture is used when vaginal examinations are made. Many of our patients who had cesarean sections had no vaginal examinations and consequently instillations were not used. Our cultures indicate that infection may be introduced through the incision as well as through the vagina. The vaginal instillations could not possibly prevent introduction of infection through the abdominal route. Another point which should be emphasized as an argument against

TABLE IX. CULTURE III

	CASES	PER CENT OF ALL
Negative	184	36.07
L. gram + diplobacillus	88	17.45
<i>Staph. albus</i>	75	14.70
Gram + diphtheroids	63	12.35
<i>Strep. diplobacillus</i>	24	4.71
Döderlein's bacillus	17	3.33
Anaerobic strep.	13	2.54
<i>B. mesentericus</i>	9	1.76
<i>B. subtilis</i>	9	1.76
Gram + rods	9	1.76
<i>Strep. hemolyticus</i>	8	1.56
<i>B. coli</i>	4	0.78
<i>Strep. proteus</i>	2	0.40
Miscellaneous	4	0.78

the performance of cesarean section after a long duration of labor is the one of trauma and exhaustion. I am opposed to eliminating the contraindication of the duration of labor from consideration in performing cesarean sections, and I do not believe that routine use of vaginal instillation would overcome this objection. I am opposed to the performance of cesarean section after a woman has been in labor over twenty-four hours either with or without previous rupture of the membranes. I do not believe that in general we can operate as safely and perform a cesarean section twenty-four hours after the onset of labor even with the routine use of vaginal instillations. Our figures for febrile morbidity and mortality are very low without the use of vaginal instillation as a routine procedure. These figures have been reported by Daily in a recent article on 1,000 cesarean sections performed at the Chicago Lying-in Hospital.*

DR. LOUIS E. PHANEUF, BOSTON, MASS.—Matthews and Acken have reported in 1,000 cesarean sections, a maternal mortality of 3.18 per cent. A lower mortality throughout the series is shown for the so-called low flap or lower segment operation. This is in keeping with other published series of the last two decades. Of particular significance are the figures demonstrating no maternal mortality in secondary low flap operations and the same mortality rate in secondary classical as in primary classical sections. Furthermore, the essayists show that during the last six years of the study there was a definite decrease in mortality in the so-called cervical cesarean section but an increase in mortality in the case of the corporeal hysterotomy.

A high mortality rate was reported in patients who had had previous gynecologic operations as these women were operated upon late in labor. Most of the dystocia resulting from former gynecologic interventions are consecutive to procedures employed on the cervix uteri, especially amputation of the cervix. Every obstetrician of experience knows that this form of cervical dystocia is difficult to overcome and that cesarean section should be resorted to early, since many hours of labor will not change the condition of the cervix, if a few hours of real labor have not softened and begun to dilate the organ. Cesarean section of election or early cesarean section should show a very low mortality in this group of cases.

*Cesarean Section. An Analysis of 1,000 Consecutive Operations. AM. J. OBST. & GYNEC. 37: 348, 1939.

In the repeat cesarean sections 5 of 11 deaths were due to intestinal obstruction, a complication which I have never met in a large series of repeated low flap operations.

Throughout the paper one is impressed with the fact that the serious infectious complications followed the classical section and that there were no deaths from sepsis in the lower segment operations. Again, fewer deaths occurred in the hands of men of greater experience than in those of younger men. This is as it should be with any form of surgical operation.

Spinal anesthesia was used in 90 cases, and the authors state that "Many clinics would do well to use it more frequently." Personally I feel that spinal anesthesia is the most dangerous form of anesthesia in cesarean section. This statement is based on facts and not on impressions. Local anesthesia may be used in all instances where spinal might be indicated and this with a marked increase in safety.

Edward A. Schumann has shown in a paper recently published in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY* that the mortality and morbidity could be markedly reduced if the operator could make up his mind to interfere early even though this might entail the performance of a few more cesarean sections. He states, "I have never regretted doing a cesarean section, but I have regretted not doing one."

The gross fetal mortality is given as 5.2 per cent. This is within ordinary limits, but shows none the less that abdominal delivery does not necessarily assure a living baby.

The best figures from the standpoint of mortality which I have been able personally to obtain gave a gross maternal mortality of 1.6 per cent in a series of 429 transverse cervical cesarean sections, and a gross fetal mortality of 2.5 per cent in the same series.

It is evident from Brown's important statistics that the instillation of antiseptics in the vagina, 1 per cent neutral acriflavine in glycerin, will definitely reduce morbidity and mortality in cesarean section. Matthews and Acken, as well as Brown, have reported similar results by the instillation of mercurochrome. Strangely enough, during my training at the Carney Hospital, I was taught meticulously to prepare the vagina before a panhysterectomy and at the New York Lying-In Hospital never to do vaginal manipulations of any kind before performing cesarean section. In view of Brown's findings, I am convinced that I will change my method of procedure in this regard.

DR. ACKEN (closing).—I should like to stress that we have instilled vaginally an ounce of 4 per cent mercurochrome every twelve hours during labor. It has not entirely eradicated sepsis but has reduced it. We agree with Adair's statement that the technique of instillation must be carried out with great care.

We accept Phaneuf's criticism concerning patients who have had a previous gynecologic operation. These patients should not be subjected to a long test of labor.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—If the instillation of a solution in the vagina decreases the incidence of infection, why not make the vaginal preparation such as is ordinarily made for abdominal hysterectomy? It would seem to me to be much more thorough and more clean.

DR. HENRY S. ACKEN, JR.—We assume that there has been no gross contamination of the vagina before delivery, and we use the mercurochrome instillation simply as a means of eradicating such infection as may have entered from the outside.

DR. BROWN (closing).—The same method of obtaining the culture was used as that described by Harris and Brown: "All of the cultures were taken through the uterine incision in order to ensure that they could not be contaminated by the vaginal secretions. As soon as the child was delivered, before the hands or the instruments had been introduced into the lower uterine segment, a sterile cotton

covered swab was passed through the uterine incision and rubbed over the uterine segment, care being taken that it did not come in contact with any portion of the uterus except that from which the culture was desired."

I might also say that the instillation that we use in preparation for cesarean section is that used routinely in all of our patients in labor. Actually it started as a routine preparation during labor. I would urge Matthews and Acken to use these instillations a little more frequently, because in checking up on the cultures of the vagina after instillations, I find that it takes from eight to ten hours for the solution to give us an actually sterile culture from the vagina. We have observed infections sometimes when the patient has been in labor for only a couple of hours after the instillation was first given. Such a patient has not received adequate care in that period of time.

THE GLYCOSURIAS OF PREGNANCY*

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THIS report consists of the impressions gained from our experience during the care of 43 pregnancies occurring in 38 diabetic patients, and 25 pregnancies in the benign type of glycosuria. These impressions are the summation arrived at by the cooperative study between the diabetic service of Dr. R. T. Woodyatt, his associate Dr. Leo Campbell, and the entire obstetric service of the Presbyterian Hospital, Chicago. The period of this analysis extends from 1921 to April, 1939.

This study was undertaken to evaluate our present methods of treatment and to determine whether a comparison of the histories of the diabetic patients with those of the nondiabetic glycosurias of pregnancy might not throw further light on some of the general principles underlying both conditions.

In view of recent basic observations in the fields of endocrinology and metabolism, these comparisons suggest new approaches to the problems of the glycosurias in the pregnant woman. The degree and rapidity of changes in glandular function during pregnancy in women produce an experimental subject that is much more intriguing than it is in the usual laboratory animal. Correlation and interpretation is, of course, more complicated and hazardous in the human being.

A survey of the antecedents of diabetics reveals a high incidence of glandular stigmas. The predominating type found among this group of mothers is that of the short individual who is spoken of familiarly in obstetric circles as belonging to the dystrophy syndrome. A study of the sizes and weights of the infants substantiates the findings of many other observers that at least diabetics and probably also the benign glycosurias are more likely to give birth to larger babies than do normal women. Approximately 60 per cent of the infants born to the diabetic mothers weighed 8 pounds or over. The largest one weighed 14 pounds 4 ounces, the smallest, which was premature, 4 pounds 5 ounces. A similar increase in the size of the fetus was noted in the nondiabetic glycosurias, although 10 pounds was the largest infant in this latter group. Heretofore we have ascribed the increased size of the baby largely to the hyperglycemia of the diabetic mother. This explanation, however, cannot be valid in the benign types of glycosuria, in which the blood sugar level is usually somewhat below normal. In like manner, if we review the previous obstetric histories of the group of diabetic women, we find that they also gave birth to a

*Presented at the Sixty-Fourth Annual Meeting of the American Gynecological Association, White Sulphur Springs, W. Va., May 22 to 24, 1939.

high percentage of giant babies *long before their clinical diabetes had become manifest*. The gain in maternal weight during these previous pregnancies, where recorded, corresponded with the gains in weight during our period of observation. Previous published clinical reports indicate that maternal dietary changes have no appreciable effect on the weight of the infant during normal pregnancy. When we compare the gain in weight of the mother directly with the weight of her baby in these groups, we find that in general the mothers who gained the most weight during pregnancy more frequently gave birth to the largest babies (Chart 1). This was particularly noticeable among the diabetics, although to a lesser extent in the nondiabetic patients. In the diabetic group, all but one of 19 mothers who weighed 150 pounds or over gave birth at term to babies weighing 8 pounds or more. More information should be acquired concerning the transmission of glucose and fat through the placenta. It has been our experience that the nondiabetic pregnancy, particularly the overweight toxemic individual, carries a fasting blood sugar which is consistently in the lower levels of normal. Furthermore, the blood sugar levels of the cord blood are usually only slightly over one-half of that of the mother. In one instance blood taken from the mother shortly after intravenous glucose solution was given contained 540 mg. of glucose while her baby's cord blood held only 60 mg. per 100 c.c. We expect to check these findings further, particularly in twin pregnancies and in animals. If we compare the average fetal weights of the undersized babies born to overweight toxemic mothers with the oversized infants of a like group of overweight toxic glycosurics, it would seem logical to conclude that other factors besides the mere ingestion of more food are responsible for this phenomenon, or that the toxemias are of a different type. We have ascribed the failure of growth of the baby in the toxemias of pregnancy to toxic conditions, particularly in the placenta. But many of the largest babies observed in our series were born to mothers who showed the severest symptoms of toxemia, and who had no gross changes in the placentas. In like manner we have all seen very small, poorly developed babies born to overweight toxic mothers with no abnormal gross or microscopic changes in the placenta to account for it.

Newburgh has stated that gain in body weight is in direct proportion to the increased ingestion of food. He believes that glandular imbalance has relatively little to do with the problems of loss or gain in body weight. It would seem to us that particularly in the diabetic pregnancy whose dietary regime is usually so strict and accurate, at least some of the marked gains of weight especially in the latter months of gestation might require additional explanation. What change occurs in the mechanism of appetite during normal pregnancy? Almost without exception pregnant women develop a desire for food which is beyond the immediate needs of the growing fetus. Proof of this is found in the extra maternal weight gain during normal gestation. It would seem to us that this mechanism has probably undergone even more marked derangement in this group of patients than in a similar number of normal pregnancies.

It has been rather definitely proved that the inheritance ratio of the diabetic tendency is high. Priscilla White has reported it at 52 per cent. She has also reported that 90 of 100 children were above average height before they became diabetic. Fundamental clinical observations as well as animal experimentation have definitely localized the impetus to somatic growth in the anterior lobe of the hypophysis. We do not see rapidity of growth illustrated as well anywhere else in animals or man as in the pregnant female. The amazing growth of the fetal elements is almost matched by the tremendous hypertrophy of the uterine apparatus. Even the accessory organs of reproduction, such as the breasts, respond to this stimulus. In addition we have the more incompletely defined pituitary functions which include carbohydrate and fat metabolism other than by the way of the thyroid, pancreas or adrenals. The recent isolation by Collip and his co-workers of a potent metabolic factor from the pituitary may be important in this general problem. May some of this change not be due to the protective slowing of the sex glands during pregnancy? A similar or appreciable gain in weight occurs regularly in the castrate or following the climacterium in both men and women. This depression of the sex glands is for the most part probably due to the increased activity of the pituitary gland. In future studies additional information is desirable and a complete family history should be obtained as far back as information is available. This history should include not only the details of familial diabetes but all evidence of glandular disease or dysfunction. Still closer controls would include the extension of family histories to include the past obstetric histories of all branches of the family tree. We have now in the hospital a fourteen-year-old boy in whom diabetes was discovered four months ago. The family history for three generations back does not reveal diabetes but a surprising number of giant fetuses and stillbirths. The average weight of our diabetic mothers at term was 159.5 pounds. Several of them weighed over 200 pounds and two reached a weight of 240 pounds. In the nondiabetic group 13 of them weighed from 160 to 225 pounds. Twelve of them weighed from 109 to 142 pounds.

Recent clinical observations by many observers have indicated that the fundamental factors controlling glandular balance may also be closely connected with the pregnancy toxemias. Marked or too rapid gains in maternal body weight frequently seem to coincide with the development of toxic states. Transient glycosurias developing during the latter half of pregnancy are often soon followed by the appearance of edema, hypertension and albuminuria. This observation was made first by Williams, and we have noted it frequently in our patients. This type of transient glycosuria is not included in the present series. In spite of the fact that no specific pancreatogenic hormone has been isolated from the pituitary, experiments, such as those initiated by Houssay, indicate that the pituitary is most intimately associated with the glycogenic equilibrium. There is a growing belief that eventually the control of a considerable number of diabetics and perhaps benign glycosurias will be carried out with other hormonal substances rather

than insulin. In light of our present knowledge the pituitary seems to be the most likely candidate for this role. Approximately 70 per cent of our number of diabetics revealed evidence of one or all of the cardinal signs of the toxemia of pregnancy. The greatest proportion of these occurred in the markedly overweight individuals. All but two of these patients who showed two or more signs of toxemia weighed from 160 to 240 pounds. Many of these toxemias were of a severe degree but none, and we feel this may be important, developed the convulsive type of toxemia. Labor was not induced in any of these patients on account of toxemic symptoms. Priscilla White found 21 per cent of 168 diabetic women during the insulin era who developed signs of pre-eclamptic toxemia, only five of whom developed convulsions. These investigators feel that the diabetic woman protects herself against eclampsia by destroying the placenta and incidentally the child, which accounts for the high incidence of stillbirth and spontaneous abortion. More recent work in their clinic indicates that a rise in serum prolactin, anterior pituitary-like hormone, and a fall of estrin preceded the clinical signs of toxemias, stillbirth and often premature delivery or miscarriage. Taylor has not been able to substantiate these findings. In spite of this we feel particularly in view of Schneider's observations on the production of giant fetuses and their increased mortality in the rabbit by the use of pituitary substances, that this general direction offers the most encouraging field for study. In our series the patients who were delivered of dead babies did not present the symptoms of severe toxemia; in fact, only two of them showed either hypertension or albuminuria. One of these had a systolic blood pressure of 158 and a trace of albumin in the urine, the other a blood pressure maximum of 140 and 3 mm. of albumin. We did not find placental pathology of a degree which we felt might have caused fetal death. Furthermore, the size of the dead babies was much larger than those found with marked placental damage in the ordinary toxemia.

The type of toxemia encountered in this series of patients was predominantly nephrotic; edema was the commonest and most marked finding. Hypertension came next in frequency, although albuminuria was noted in eight of the diabetic and three of the renal glycosurias. Herriek and Tillman have noted as significant the frequent association of diabetes and the vascular type of toxemia. Diabetics in general are very likely to develop vascular lesions of a marked degree. In view of the unusually high incidence of toxic symptoms in these patients the question might be raised as to whether they are largely the result of these vascular changes, disturbances in glycogenic equilibrium or are more probably another symptom of the fundamental glandular dysfunction which also causes the glycosuria. Most accurate insulin control seems to be inadequate in preventing or allaying the symptoms of this toxemia of pregnancy.

It is quite evident from a study of the literature that insulin has accomplished relatively little in lowering the fetal death rate. The main benefit has been in lowering the number of maternal deaths to approximately the normal incidence in pregnancy. The fetal death

rate even for the insulin era is appallingly high. A résumé of the obstetric histories of the diabetic patients before they came under our observation records 13 stillbirths and 13 miscarriages in a total of 85 pregnancies. During our attention, while on accurate diabetic management, these 43 pregnancies ended in stillbirths six times and 7 of the abortions were done therapeutically. We cannot be greatly impressed by the fetal life-saving properties of insulin.

A critical study of our records indicates that the majority of the term fetal accidents were not due to obstetric causes. Nor, as we have already indicated, do we feel that they were directly connected with the high incidence of toxemia. It may be possible that too accurate control of the diabetes has produced a fatal hypoglycemia in the fetus, but we doubt it. All possible steps have been taken to prevent this catastrophe. These steps include the giving of glucose solution by bottle and nipple immediately after birth, as suggested by Randall, and maintaining an adequate maternal glycosuria during pregnancy. There is a great need for more detailed studies of the fetal and maternal blood sugars during the last few weeks of pregnancy, during and immediately following labor. The antenatal and intra-partum accidents to the baby were about equally divided in the diabetic group of patients. This mortality was six times as frequent as in the benign type of glycosuria. The appearance of fetal abnormalities was the same in both groups.

The insulin requirements of most if not all of our patients was increased as pregnancy progressed. It would seem that in the human female at least the production of insulin by the fetal pancreas does not usually compensate for the increased demands on the maternal organism. On the contrary, the insulin requirement often falls rapidly after labor is over. The most frequent insulin reactions in this group occurred in the first four days of the puerperium. This in large measure is most likely due to the insult of labor and delivery, but one may speculate that the same mechanism is also operating which at this same time restores normal maternal water balance and promotes the activity of the breast. One may wonder whether a negative Aschheim-Zondek test appearing at about this same time is not significant. These questions may well be asked when we study the puerperal and labor records of these patients. Judged by the usual standards there were 56 patients who had an uneventful afebrile convalescence. Three of the diabetics and one of the simple glycosurias had elevations of temperature. All of these patients left the hospital well at the usual time. It was not in this last group of patients nor in those who had the longest and more traumatic labors where the largest number of insulin reactions occurred during the puerperium.

We may speculate further on the appearance of acetone bodies in the urine of these patients. The persistence of these bodies on an adequately balanced diet, as high as 2,000 calories, for several days suggests an additional factor to that found in normal pregnancy where acetonuria may occur even with normal sugar consumption. One is reminded of the experiments of Anselmino and Hoffman who showed that alkaline

TABLE I. LIVING BIRTHS

AGE	DURATION DIABETES MONTHS	WEIGHT	LABOR	INFANT
DIABETICS				
27	18	101	4:45	6-12
22	2	110	Spont.	6-10
32	30	120	3:30	8-5
31	84	121	14:45	7-15
26	72	130	7:45	6-12
28	114	134	6:30	4-14
27	48	135	4:30	4-5
28	120	135	20 (L.F.)	9-15
24	15	143	L. cerv. sec.	5-15
30	24	145	12	8-7
30	2	146	2	7-13
30	12	148	14	8-6
29	72	150	13	10-3
30	84	150	40 (Duhr.)	8-5
29	60	151	7	6-2
44	192	154	Porro	8-14
27	24	160	2:30	8-5
33	17	162	4:30 (cas. oil- quinine)	9-8
24	96	163	L. cerv. sec.	8-12
24	2	170	12 (M.F.)	8-10
24	5	174	25:45	8-0
25	17	179	8:45	8-1.3
43	3	181	4:30	11-1
25	3	184	14	5-14 (8 mo.)
24	24	185	9:30	10-0
29	12	198	7	9-0
37	3	240	3	11-2
GLYCOSURIAS				
26				6-10
26	21 days	109	C. Sec. c. p.	
31	120	126	11	4-5
				(1 mo. premature)
19	15 days	128	7:25	8-6
28	1	128	C. Sec. (prev. sec.- c.p.)	8-15
29	3	133	5	8-12
24	1	134	5:50	7-3
29		134		6-3
24		136	13:20	8-9
39	6	139	12:30 (M.F.)	8-2
29		142	2:20	9-6
29	7 days	160	3	9-1
35	6	164	4	4-15 prem.
33		165	17	7-3
38	4	165	10	10-0
33	5	168	9:30	6-13
26	21 days	170	6:20	8-12
29		174	3:45	9-2
21	21 days	181	4 (L.F.)	8-15
28	20	184	4	8-6
23	36	195	10 (Died 23 days later)	8-1
38	9	207	4:30	7-1

TABLE II. RECORD OF FETAL ACCIDENTS

CASE	AGE	DURATION DIABETES	HEIGHT MA- TERNAL WEIGHT	PREVIOUS OBSTETRICS	PRESENT OBSTETRICS
1	25	4 months B.P. 158 Albumin, trace	5 ft.-6 207.5	12 lb., normal 3 yr. ago Spontaneous abortion 2 years ago	Began labor 5:45 P.M. Break- fast, pancakes and syrup. Urine free of sugar on ad- mittance. Delivered still- born, 14 pound 4 ounce baby at 8:55 P.M. Heart tones rapidly disappeared when dilatation practically complete. Forceps delivery for failing heart tones. No obstetric cause of fetal death. First insulin, 8 units, at 12 P.M. following delivery.
2	40	3-4 mo. Sympto- matic B.P. 140/90 3 mm. albumin	238.5 280 four years ago	First husband—mar- ried at 15 1 girl, normal 1 girl, normal 1 boy, normal 1 miscarriage Second husband—7 yr. ago 1. miscarriage 2. miscarriage 3. boy, heart dis- ease O.K. 4. miscarriage 5. twins born dead	Heart tones not heard on ad- mittance. Patient having dark brown discharge. Fetus badly macerated. Had not been on insulin previously. Six months term—3 pounds 15 ounces. Insulin—8-10-10- 10. Urine 0.17-2.607.
3	27	1½ mo. B.P. 120/80 No alb.	4 ft.-11 153.5	1923, 7 lb. normal girl 1926, dead baby 1931, dead baby 1934, dead baby	Intrauterine fetal death 24 hours before labor began. Cord around neck twice. Ba- by weighed 8 pounds 9 ounces. No insulin.
4	40	1½ yr. B.P. 120/92 No alb.	5 ft. 2½ 196½	1916, Stillbirth, 3 hr. labor 1917, Normal, 9½ pounds 1919, Normal In between 7 babies weighing from 8 to 10 pounds 1930, Stillbirth, 14 pounds	Normal delivery, labor 6 hr. 40 min. Insulin 16 units. Died 3 days later, intestinal atresia, weight 10 pounds 10 ounces. Patient had severe pituitrin reaction following delivery.
5	25	3 mo. B.P. 124/90 No alb.	137	Normal delivery, 6¾ pounds, 3 weeks premature Maternal hyperten- sion and albumin- uria	Neonatal fetal death, probably several days. Eight months term. Discharged {Prot. 14 Reg. 4 Baby weighed 9 pounds 7 ounces.
6	33	9 yr. B.P. 120/68 No alb.	146	None	Bag induction followed by ar- tificial rupture of mem- branes; three-fourths dilata- tion of cervix, sudden disap- pearance heart tones. Crani- otomy, fetus, 9 pounds; short cord, 12 inches. Insulin 22- 22-22-22; 1966 cal. Urine 2.21-48.6.
7	31	4 mo. B.P. 120/80 No alb.	165	1. 7 pounds, died at 2 mo. 2. 7 pounds, normal 3. 7 pounds, died at birth 4. 10 pounds 11 ounces, O.K.	Ante-partum fetal death, prob- ably at onset of labor. Weight 10 pounds 5 oz. Di- abetes treated 4 months of pregnancy. Insulin 4-4-4. Fetal blood sugar 0.08. Urine, 2.93-11.84.

extracts of the hypophysis will produce an acetonuria. On the other hand, Houssay has shown that hypophysectomy will eliminate ketosis. Long has repeated this by removing the adrenal glands.

TABLE III

NO. OF INFANTS	WEIGHT POUNDS	PERCENTAGE
<i>Diabetic Babies Living and Stillborn</i>		
2	4- 5	6.0
2	5- 6	6.0
4	6- 7	12.1
2	7- 8	6.0
11	8- 9	33.3
5	9-10	15.1
4	10-11	12.1
2	11-12	6.1
1	14-15	3.0
<i>Glycosuric Babies Living</i>		
2	4- 5	9.5
3	6- 7	14.2
3	7- 8	14.2
9	8- 9	42.8
3	9-10	14.2
1	10-11	4.7
<i>Average Weight of 4,622 Infants Born in Presbyterian Hospital From 1930 to 1939</i>		
NO. OF POUNDS		PERCENTAGE
5- 6		6.0
6- 7		24.1
7- 8		38.0
8- 9		24.0
9-10		7.0
10-11		0.9
<i>Diabetic Stillbirths</i>		
Average age of mothers		31.8 years
Average weight of mothers		179.1 pounds
Average weight of 6 infants		10.6 pounds
Average duration of disease		27.9 months
Average duration of labor		14.1 hours
Weight of infants		
1 infant	8- 9 pounds	16.6 per cent
2 infants	9-10 pounds	33.3 per cent
2 infants	10-11 pounds	33.3 per cent
1 infant	14- 4 pounds	16.6 per cent
<i>Diabetic Abortions</i>		
Average age of 8 mothers		27.5 years
Average weight of 5 mothers		114.6 pounds
Average duration of disease, 5 mothers		29.6 months
Treatment		
1 spontaneous		
5 dilatation and curettage		
1 dilatation and curettage, and sterilization		
1 hysterotomy		
1 hysterectomy		
Mortality		
1 died of tuberculosis		

TABLE IV

DIABETICS					GLYCOSURIAS				
AGE	DURATION DIA- BETES	WEIGHT	LABOR	INFANT	AGE	DURATION SUGAR	WEIGHT	LABOR	IN- FANT
<i>Stillbirths</i>									
26	3	136	7 (castor oil and quinine)	9-7	36		180		
33	108	146	38 (bag, high forceps, craniotomy)	9-0			Not delivered here		
28		153	13 (cord around neck)	8-9	20	4 ?	225		
31	7	165	18	10-5	29		134		
24	3	207	12 (midfor- ceps)	14-4					
41	18	207	6	10-10					
40	28 yr. ?	240	5	Macer- ated					
<i>Abortions</i>									
23	12	118	Hysterectomy, 6 wk.						
23	14	125	Aborted elsewhere. In- complete D. and C. D. and C., 2 mo.						
24									
24		110	D. and C., 3 mo. Died tuberculosis						
26	60	112	D. and C., 2 mo.						
29		108	Therapeutic D. and C.						
31	24		D. and C., steril., 2½ mo.						
40	38		Hysterotomy, 6 mo. Spont., 4 mo.						

In spite of the predominance of overweight babies the average length of labor in our diabetic patients was 9.3 hours, that of the benign glycosurias 7.4 hours. Spontaneous birth occurred 44 times and 6 babies were delivered with forceps in the combined group. The one craniotomy was performed to prevent maternal damage during delivery of a baby which was already dead in utero. Cesarean section was resorted to 5 times, mostly for obstetric reasons (contracted pelvis), although occasionally the increased size of the fetus was an important deciding factor. Several of the stillbirths might have been prevented by cesarean section. However, when we carefully analyze not only the present but also the past obstetric history of these 4 cases, we are impressed with several pertinent facts.

Two of the antenatal deaths occurred at eight months' gestation. Cesarean section would of necessity have had to be performed before this time to have saved these babies.

Nine of the 13 stillbirths recorded in the previous obstetric histories of the entire group occurred in 4 of the 6 patients who lost 3 babies while under our attention. These previous stillbirths, usually of large babies, occurred long before the patient had developed clinical diabetes. This fact suggests that glycosuria is only another or perhaps

later manifestation of a condition that may produce larger babies and sometimes kill them before birth. All but one of these last mentioned patients were mild diabetics as judged by their insulin requirements and degree of glycosuria. One had had no insulin during labor.

We would suggest, therefore, that cesarean section as a method of delivery for diabetics should probably be reserved for:

1. Strict obstetric indications.
2. Those in whom sterilization is urgently indicated.
3. Those patients in whom the previous obstetric history reveals a previous still-birth which was not due to the usual obstetric complications.

A comparative résumé also indicates that the increased tendency toward toxemia, ketosis and unstable glandular equilibrium are further evidences of a common derangement that may have its beginning in the hypophysis or vegetative nervous system.

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55 E. WASHINGTON STREET

DISCUSSION

DR. WILLIAM J. DIECKMANN, CHICAGO, ILL.—It is obvious from Allen's excellent presentation that insulin is not complete replacement therapy. The non-pregnant diabetic properly treated is still subject to a higher incidence of arterial disease than the nondiabetic and may also develop the apparently specific fatty degeneration of the liver. The fetal mortality as reported by Allen and others really shows that even properly controlled diabetes in pregnancy is accompanied by a fetal mortality much greater than normal.

Our treatment has been similar to that described by Allen. We believe that the diabetic patient should be told of the seriousness of her condition. If the patient has several other children, the management of her own diabetes at times becomes quite an economic problem; therefore if the patient is seen early in pregnancy these various conditions are discussed with her and therapeutic abortion and sterilization are used freely.

The question as to what constitutes glycosuria in pregnancy is quite an important one. I have not been able to find a satisfactory definition of it in any of the textbooks or published articles. Woodward, with whom Allen has worked, has a definition for it, but to fulfill the requirements hospitalization is necessary. In March of this year 1,375 urine specimens of pregnant patients were examined and 7 per cent gave a positive reduction with Benedict's solution. These urines are fermented and if subsequent urines are also positive a glucose tolerance test is carried out. In a period of one year, 65 sugar tolerances were done in our laboratory. Only five had normal curves and negative urines. Only 19 had normal curves, but the urines always contained sugar. Sixteen of the curves were typical for diabetes. In a six-month period we had 9 pregnant diabetic patients, an incidence of 0.66 per cent as compared with the incidence of 0.1 reported by Potter and Adair. During the same period in the hospital, 1.2 per cent were found to have a nondiabetic glycosuria.

DR. JOSEPH L. BAER, CHICAGO, ILL.—There are always two patients to be considered in pregnancy. This is especially so when the woman is diabetic. I am in

complete accord with Allen that the proper treatment for the bad diabetic who has had disasters in other pregnancies is early section, primarily to forestall intra-uterine death of the fetus.

Many of the fetal deaths are neonatal, occurring in the first twenty-four hours after the birth of a living fetus, and they are due to a hypoglycemia. Allweiss of the Michael Reese Hospital has demonstrated by careful studies that the hypoglycemia of these newborn infants may often be arrested with glucose injections and in that way many of the infants can be saved who might otherwise die.

DR. RUDOLPH BARTHOLOMEW, ATLANTA, GA.—Considering that diabetic patients generally show a high cholesterol content in the blood, I have a feeling that the tendency to increased toxemia and intrauterine fetal death in these cases in the latter part of pregnancy is due to changes in the placental vessels due to cholesterol.

I recall an x-ray picture of a diabetic patient, taken in the eighth month of pregnancy, which showed very distinctly the exact location of the placenta, from the arteriosclerotic changes and calcium deposits in the placental vessels. It seems to me the high incidence of intrauterine fetal death might well be attributed to the narrowing and closure of these vessels by cholesterol and calcium deposits.

In relation to the definite increase in the incidence of toxemia, as pointed out by a number of observers, it is very interesting that Hunt, Patterson, and Nicodemus fed rabbits cholesterol and subsequently allowed them to become pregnant and removed the thyroid early in pregnancy. These rabbits developed convulsions near the end of pregnancy and the placentas showed typical dark areas of acute infarction. Many of the placental vessels were almost occluded by the lipoid cells beneath the endothelium. The control rabbits which were fed cholesterol but were not thyroidectomized early in pregnancy, had no convulsions or acute placental infarcts.

DR. ALLEN (closing).—We have felt that perhaps our therapeutic abortions were rather frequent. Many of them, however, were done for patients who were either too low mentally to follow accurately diabetic treatment, or even refused to do so. Some of them had a familial history of diabetes on both sides of the family.

There were no infant deaths in this series after birth. We have for quite a while followed the plan suggested by Baer of giving the fetus glucose immediately after birth and maintaining an adequate output of sugar from the mother during labor. There did not seem to be any suggestive findings in the cholesterol values in the series we examined. I think there is a difference in the cholesterol values in the rodent and in the human being. Yet with this glandular disturbance one might expect an increase in the cholesterol values in a certain number of cases.

OCCIPUT POSTERIOR*

INCIDENCE, SIGNIFICANCE, AND MANAGEMENT

L. A. CALKINS, M.D., PH.D., KANSAS CITY, MO.

(From the Department of Obstetrics and Gynecology, University of Kansas)

THE excellent presentations on occiput posterior by Norris W. Vaux in 1930, and A. H. Bill in 1931, led us to analyze our own experience. Our attitude toward occiput posterior and our experience in its management had been considerably different. We wondered whether our failure to deliver our patients, as soon as the cervix was dilated, had resulted in a higher fetal mortality or maternal morbidity than that indicated in these two papers. We observed that the medical profession, both general practitioners and specialists, had rather suddenly acquired a certain "occiput posterior consciousness" and dread of this position. Ill-advised attempts at delivery, even before the cervix was completely dilated, were resulting in stillbirths in rather alarming numbers. Physicians were willing to accept Vaux's recommendation of version or Bill's recommendation of Scanzoni forceps, but they sometimes failed to note that in both cases interference was not recommended until the cervix was fully dilated. This "fear" of occiput posterior has resulted in four intranatal stillbirths in this present series. Interference was undertaken by the physician with the cervix only about half dilated and delivery was attempted by forceful traction with forceps extending over a period of one to three hours after which the patient was sent to our institution.

In attempting to analyze our experience we soon found that our diagnoses of position were not sufficiently accurate to permit a critical analysis. We had been reasonably careful in making these diagnoses, but there were too many instances where the examination had been made by an intern and had not been checked by a more experienced observer. In other patients the attending man had arrived rather late and, because external rotation was toward the left, had decided that the presentation must have been O. L. A. In some cases the patient had arrived at the hospital rather late in labor with the cervix considerably dilated and the head at, or near, the pelvic floor. We therefore decided that, if accurate statistics as to the incidence of occiput posterior were to be obtained, we must have a more rigid and clear-cut system for arriving at the proper diagnosis. We also realized that unless we knew accurately the incidence of occiput posterior we could not come to a rational conclusion as to the results or proper methods of management. We therefore started in 1933 to collect an accurate series of cases and have rigidly adhered to the following plan of diagnosis: (1) The diagnosis should be made by internal examination

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(rectal or vaginal) (in addition to the usual abdominal palpation) by careful palpation of the suture lines and fontanels; (2) The diagnosis of the intern should not be accepted unless checked by a more experienced observer; (3) The diagnosis should be made as early in labor as possible and should be checked repeatedly at intervals in the labor; (4) If, when the patient was first seen the labor had progressed to complete dilatation and the presenting point was at, or near, the pelvic floor, no diagnosis except "unclassified cephalic" should be made.

Since the inception of this plan we believe we have a more accurate idea of the frequency of the various positions than ever before. We have not, of course, been able to eliminate all errors in diagnosis, but we feel that the gross error in our present figures is probably not greater than 5 per cent. It should be noted that of the total of 2,446 patients here reported, 131 are classified as "cephalic." This includes not only patients who were seen late in labor but also others upon whom the diagnosis had not been accurately made, either owing to a large caput or through paucity of examinations. It is thought that several of these were actually occiput posterior, but the diagnosis could not be accurately established.

One hundred and eighty-five patients had diagnoses of brow, face, bregma, shoulder, breech, or twins and therefore have been excluded from this discussion of occiput presentations. This leaves a total of 2,130 occiput presentations in which the diagnoses were carefully made and therefore are considered reliable for accurate classification. In each instance the direction of the sagittal suture and the position of the posterior fontanel were recorded on the chart early in labor. In a vast majority of these cases this record was made previous to six centimeters dilatation. We have considered as occiput anterior only those cases where the sagittal suture was anterior to, or exactly in the transverse, and we have similarly designated as occiput posterior only those cases where the small fontanel was actually posterior to the transverse diameter of the pelvis. We believe this classification is simpler than that more complex one where transverse positions are recognized and recorded therefore making six groups instead of four.*

INCIDENCE OF POSITIONS

Our records since using this method of diagnosis and plan of classification are shown in Table I.

These figures stand in sharp contrast with those reported by others. O.D.A. in this series is decidedly the least common position, instead of ranking next in frequency to O.L.A. O.L.P. is much more common than previously noted except in

*Our cases were so recorded, however, that a classification into the anterior, transverse, and posterior is readily available and we offer it in the table below for purposes of comparison with other authors' series.

	PRIMIPARAS	MULTIPARAS	TOTAL
O.L.A.	344	205	549
O.L.T.	214	98	312
O.L.P.	100	36	136
O.D.P.	256	123	379
O.D.T.	165	78	243
O.D.A.	44	25	69

TABLE I

		TOTAL
O.L.A.	939	
O.D.P.	702	
O.L.P.	326	2,130
O.D.A.	163	

Vaux's series. Presentation in the left oblique diameter occurred 489 times, as against 1,641 cases in the right oblique diameter. This is in line with previous statements. The striking thing, however, is that there are 1,028 cases of occiput posterior as against 1,102 cases of occiput anterior. In primiparas, occiput posterior actually occurred a few more times (687) than occiput anterior (677). From a strictly biologic point of view, it would hardly seem possible that occiput posterior could be a very distinct abnormality if it occurs with equal, or almost equal frequency with occiput anterior. It is our firm conviction that if diagnoses are made with the care indicated above occiput posterior will be found to occur with almost equal frequency with occiput anterior and that the four positions will occur roughly as follows:

O.L.A.	5+
O.D.P.	4
O.L.P.	2
O.D.A.	1
Total	12+

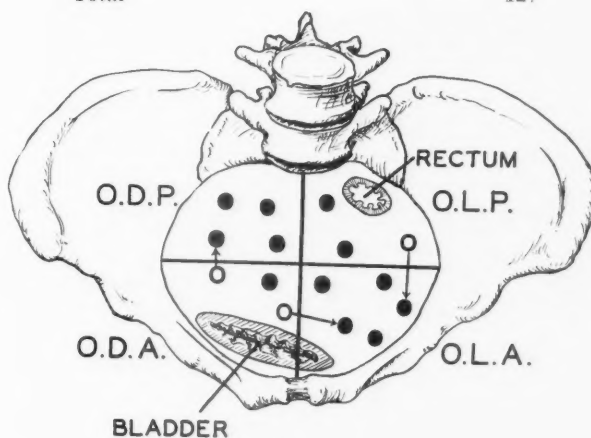


Fig. 1.

In a previous publication³ we attempted to explain this relative incidence on the basis that the presence of the rectum in the left posterior quadrant of the pelvis tended to prevent the occurrence of O.L.P. in about one-third of the cases where it might, otherwise, have occurred if governed only by pure chance (Fig. 1). We further stated that the presence of the bladder in the right anterior quadrant of the pelvis tended to prevent the occurrence of O.D.A. in about two-thirds of the instances where it might have occurred were no inhibiting factor present. Dextrotorsion of the uterus may also have something to do with the more frequent occurrence of presentations in the right oblique diameter of the pelvis.

FETAL MORTALITY

In the 2,130 cases in this series, there were 77 fetal deaths. This figure included ante-partum deaths, as well as stillbirths and neonatal deaths. This is a fetal mortal-

ity rate of 3.6 per cent. In 1,102 occiput anteriors there were 48 fetal and newborn deaths, a rate of 4.3 per cent, whereas in 1,028 occiput posteriors, 29 babies were lost, a rate of 2.8 per cent. Believing that occiput anterior is not actually more dangerous for the baby than is occiput posterior, we have tried to analyze this fetal mortality rate. If we exclude ante-partum deaths, we have the figures as shown in Table II.

TABLE II

	CASES	DEATHS	RATE
Occiput anterior	1084	30	2.8%
Occiput posterior	1024	25	2.4%

Among primiparas there were 677 occiput anteriors with a loss of 23 babies, a rate of 3.4 per cent; whereas in 687 occiput posteriors, 19 babies were lost, a rate of 2.8 per cent. If white primiparas only were considered, 518 occiput anteriors with 16 infant deaths showed a loss of 3.1 per cent. Twelve babies out of the 574 occiput posteriors were lost, giving a rate of 2.1 per cent, the lowest I have ever seen except that of Dr. Bill's privately conducted cases.* The slightly more favorable fetal mortality rate for occiput posterior as indicated by these figures would not necessarily be repeated in another similar series. We believe, however, that any properly conducted series of cases will not show a rate unfavorable to occiput posterior.†

MATERNAL MORBIDITY

We employed the American Committee on Maternal Welfare standard for computing morbidity and found 147 of the 1,102 occiput anteriors abnormal by this standard. This is a rate of 13.3 per cent. The occiput posterior cases showed very similar figures: 146 out of 1,028, a rate of 14.2 per cent. Occiput right posterior showed an identical rate with occiput left anterior. The O.L.P. cases had a somewhat higher rate, 15.6 per cent. Whether this difference is enough to be significant would seem to be open to question. Among primiparas the difference is a little greater: Occiput anterior, 14.6; occiput posterior, 17.3, the occiput left posterior presentation being again responsible for the difference. This difference is not nearly so great as that between white and colored persons. Our over-all rate for 1,092 white patients was 15 per cent; for the 272 colored patients, 19.9 per cent. If there is any increased morbidity incidental to occiput posterior, the difference is not great and it would seem to be of little practical importance.‡

*This series is about four-fifths clinical and one-fifth private; about four-fifths white and one-fifth colored

‡Causes of Fetal Mortality:

Prematurity	15
Placenta previa and premature separation	14
Severe toxemia	13
Syphilis	9
Trauma	7
Anomaly	3
Prolapsed cord	2
Miscellaneous and unknown	14
Total	77

‡The types of morbidity in this series were as follows:

	PELVIC	NO DIAGNOSIS	EXTRA PELVIC	TOTAL
Primiparas O.L.A.	9	39	35	83
O.D.P.	7	35	31	73
O.L.P.	7	14	25	46
O.D.A.	0	6	10	16
Multiparas O.L.A.	7	14	22	43
O.D.P.	3	6	12	21
O.L.P.	0	3	2	5
O.D.A.	1	1	3	5

There were 4 deaths: 1 primipara, O.D.P.: G.C. peritonitis (proved at autopsy); 1 primipara, O.L.P.: temperature 104° F. on admission, eclampsia, aspiration abscess of lung (autopsy); 1 multipara, O.L.A.: admitted with broken neck from automobile accident; 1 multipara, O.D.A.: eclampsia.

LENGTH OF LABOR

Primiparas.—The average length of the first stage of labor for occiput anteriors was 10.8 hours; for occiput posteriors 12.5 hours. This is a very definite difference, but considerably less than the figures usually quoted. Williams⁴ also felt that the difference is small. Careful inspection of these data further reveals that a large part of this difference in the averages is due to the fact that a first stage labor prolonged beyond twenty-four hours was more common in occiput posterior than in occiput anterior. Thirty-seven of our 668 occiput anteriors had a first stage of twenty-four hours or more (5.5 per cent of the cases); whereas 58 of the occiput posteriors had a similar prolongation of the first stage (8.6 per cent). We offer no explanation of the greater frequency of prolonged first stage at this time, for it will require considerable further study. If we eliminate these instances of prolonged labor, we find the average of the remaining 631 occiput anteriors to be 9.6 hours, and the 615 occiput posteriors 10.1 hours. This small difference of one-half hour could hardly be considered to be of very great clinical importance. The second stage showed a small comparative difference between occiput anterior and occiput posterior. Of the 554 occiput anteriors delivered spontaneously, the average duration of the second stage of labor was 51.9 minutes, while the average for the 534 occiput posteriors delivered spontaneously was 65.3—a difference of about thirteen minutes. Here again, however, we noted that prolongation of the second stage beyond two hours was more common in occiput posterior (52 instances) than in occiput anterior (25 instances). It would seem that "poor labor pains" is the most frequent explanation of prolongation of the second stage, but it is our impression at present that there are other factors which should also be considered. If we eliminate these few cases of prolonged second stage, the average of the occiput anteriors is 47.2 minutes and of the occiput posteriors, 52.8, a difference of only five and one-half minutes, which is a negligible quantity.

Multiparas.—The average duration of the first stage in occiput anterior was 6.8 hours; in occiput posterior, 7.7 hours. This difference of about one hour seems to be quite constant and the explanation is not to be found in the incidence of prolonged labor. There were only nine instances in which the first stage exceeded twenty-four hours in occiput posterior. The duration of the second stage of those spontaneously delivered (all but 30 of the 736 cases) was 19.6 minutes in occiput anterior and 24.6 minutes in occiput posterior, a difference of five minutes.

In primiparas therefore, occiput posteriors have a first stage about one and one-half hours longer than occiput anteriors and cause a second stage prolongation of about thirteen minutes. In multiparas the first stage is one hour longer, and the second stage five minutes longer. At least part of the reason for the longer average first stage in primiparas is the fact that truly prolonged labor (more than twenty-four hours) is more common in occiput posterior.

OPERATIVE DELIVERY

The number of operative deliveries in our multiparas was too small to permit any accurate analysis. Among the primiparas we have been perhaps too liberal in the use of low forceps and stand ready to accept any criticism on that score. Among the 1,364 primiparas there were fifteen cesarean sections, all done for elective reasons and in no instance because of the presentation. Of 1,341 primiparas delivered spontaneously or by vaginal operative procedure (excluding eight cases with incomplete records) we find that 1,088 were delivered spontaneously; twenty-two by median

TABLE III

	TOTAL	SPONTANEOUS	OPERATIVE	% OPERATIVE
O.L.A.	563	467	96	17.1
O.D.P.	437	364	73	16.6
O.L.P.	236	170	66	27.9
O.D.A.	105	87	18	17.1

forceps; 225 by low forceps; three by version; three by craniotomy. Among the occiput anteriors, there were 114 operative deliveries as against 139 among the occiput posteriors. It would seem that occiput left posterior required assistance more often than occiput right posterior.

It should be noted that the same discrepancy, unfavorable to O.L.P., was true of the length of labor (13.1 hours for the first stage, as against 12.1 hours of O.D.P.). In the last year we have learned that it is even more important to keep the bladder empty in O.L.P. presentation than in any of the other three. Perhaps if we had been more diligent in this respect as this series of cases was being observed, the average length of the first stage of O.L.P. might have been considerably reduced and fewer operative deliveries might have been found necessary. Our present attitude is that operative interference in occiput right posterior should not be more frequently necessary than in occiput anterior. If the first stage and the early part of the second stage of labor in O.L.P. be very carefully managed, operative intervention should be indicated with slightly greater frequency than in occiput anterior.

INTERNAL ROTATION

Primiparas.—Spontaneous internal rotation occurred in 539 of the 563 O.L.A.'s (95.7 per cent). Two of the remaining 24 patients delivered spontaneously without rotation. In 4 patients, median forceps rotation and delivery and in the other 18 low forceps rotation and delivery were the procedures used. In not all of these could it be said that the position "persisted." In one patient delivery was done after the patient was in the second stage only twelve minutes, and another had only fifteen minutes of second stage pains. In the majority of these 22 operative deliveries, the patient had been in the second stage at least one hour and in a few cases much longer. It would seem logical to state that in this series failure of spontaneous internal rotation occurred in about 4 per cent of the O.L.A. presentations. In O.D.A. six patients failed to produce spontaneous internal rotation. Three of these were delivered spontaneously and the others with low forceps rotation and delivery. The shortest second stage was thirty-three minutes and 3 of the 6 patients were in the second stage more than one hour, the longest being a neglected case with five hours of second stage pains. Again, fully 4 per cent failed to exhibit spontaneous internal rotation.

In the O.D.P. cases, 410 of the 437 patients had spontaneous internal rotation, 93.8 per cent. Of the remaining 27 patients, 8 delivered spontaneously with the occiput posterior. The second stage (in these 8) varied in length from twenty-two minutes to two hours and twenty minutes. Six of the 8 patients had second stages of one and one-half hours or less. The remaining 19 patients were delivered by operative procedure: Six median forceps and 13 low forceps. It should be noted, however, that one of these patients was delivered after only three minutes in the second stage and 2 others after only thirty minutes. Two babies in this group were lost; one had been dead several days before the onset of labor and the other was in a patient with complete placenta previa. There was no difficulty in the labor of this latter case. Low forceps were used to lift the head over the perineum after a seventy-nine-minute second stage. Careful study of these 27 unrotated occiput right posteriors would seem to indicate that "persistent" occiput posterior on the right side occurs in about $4\frac{1}{2}$ per cent of primiparas, and in one-third of these spontaneous delivery can be expected after a relatively short second stage.

In the O.L.P. patients, 19 (8.0 per cent) of the 236 patients either delivered spontaneously in the posterior position (six instances) or were delivered by operative procedure before internal rotation had taken place. One of these was median forceps and the other 12 were low forceps. Three of these patients had been in the second stage less than one-half hour and delivery was undertaken because of disturbance of the fetal heart. Approximately 6 per cent, then, of occiput left posterior in primiparas either failed to undergo spontaneous internal rotation or were delivered before such rotation had taken place. Nearly half of these were delivered spontaneously and there was only one fetal death in this group. The

local physician had tried for two hours to deliver the patient with forceps when the cervix was only 4 cm. dilated and then, after death of the baby, had sent the patient into our institution.

It might be pointed out that in 9 of the occiput right posteriors and 4 of the occiput left posteriors the low forceps delivery was done without rotation of the head, without serious trauma to the mother, and with no apparent injury to the baby. The delivery was easily accomplished in each of the 13 cases. (Respective birth weights: 2,565, 2,835, 2,865, 2,880, 3,025, 3,070, 3,100, 3,140, 3,175, 3,410, 3,425, 3,575, and 4,030 gm.)

In compiling these records we did not at first realize the importance of noting whether spontaneous internal rotation always occurred in the occiput anterior cases and hence the figures, above quoted, no doubt represent a somewhat more frequent occurrence of spontaneous internal rotation in occiput anterior than was actually the case. In the last two years we have noted that a number of these patients delivered without internal rotation. So far as this series shows, it would seem that spontaneous internal rotation occurred in about 96 per cent of occiput anterior and about 95 per cent of occiput posterior. Operative delivery is necessary, *perhaps because of failure of rotation*, in about 3 per cent of occiput anteriors and 3 to 3.5 per cent of occiput posteriors.

Multiparas.—Among the multiparas there were 4 O.D.A.'s, 3 O.L.A.'s, 5 O.L.P.'s, and 13 O.D.P.'s which either failed to rotate spontaneously or were delivered before rotation took place. Eighteen of these patients delivered spontaneously. There were 5 median forceps and 2 low forceps with only 1 fetal death and that, again, was due to an unsuccessful forceps before admission to the hospital. Failure of spontaneous internal rotation could not be said to have been a problem in more than 1 per cent of the multiparas in this series.

TIME OF SPONTANEOUS INTERNAL ROTATION

Primiparas.—A careful attempt was made to note the exact time at which internal rotation took place and in 1,138 patients out of the 1,364 the records showed rather clearly when rotation occurred. In 276 it was accomplished at or before complete dilatation of the cervix, in 398 during the descent of the head to the pelvic floor, in 393 only after the head had been on the pelvic floor for some time and in 71 spontaneous internal rotation did not take place. The proportion occurring at the various stages was roughly the same for all positions except O.D.A. where rotation was rarely produced until the head was on the pelvic floor or coming through the vulva. The fact that over 400 of the 1,364 patients did not show internal rotation until after the head was on the pelvic floor seems to us quite significant.

SUMMARY

Occiput posterior and occiput anterior occurred with about equal frequency in this series of 2,130 cases, where more than the usual care was taken to arrive at an early and accurate diagnosis. Occiput posterior was characterized by a somewhat longer first stage of labor. The difference, however, is not over one to one and one-half hours and the first stage in occiput right posterior is probably not much, if any, longer than in occiput anterior. The difference in the second stage is a matter of a few minutes only. Operative delivery, particularly low forceps, is more frequent in occiput left posterior than in the other three positions by about three cases in each one hundred. Fetal mortality is no greater in occiput posterior than in occiput anterior under the plan of management employed for this series. It should be noted that no pituitary extract was given previous to the delivery of the placenta and anesthesia was confined to nitrous oxide plus morphine on

indication. Maternal morbidity was about 3 per cent greater for occiput left posterior than for the other three positions. Spontaneous internal rotation occurred in about 94 per cent of occiput posterior as compared with not over 96 per cent of occiput anterior. Inasmuch as nearly half of the unrotated babies were delivered spontaneously without injury to the mother and without a single fetal death, the problem of failure of spontaneous internal rotation would seem to be not greater than 3 per cent for occiput anterior and 3.5 per cent for occiput posterior. Our present attitude toward occiput posterior is identical to our attitude toward occiput anterior, except that we realize that patience to the extent of about one hour more of waiting is required. Williams⁴ has, previously, expressed a similar attitude.

CONCLUSIONS

We should not want to give the impression that we believe that trouble is never encountered with occiput posterior. What we would like to point out is that trouble occurs with occiput anterior almost as commonly as with occiput posterior (3 per cent compared to 3.5 per cent). We also feel that inability of the patient to deliver herself spontaneously of an occiput posterior is due to causes other than the occipitoposterior presentation.

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DISCUSSION

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—When only a few cases are reported, from a statistical standpoint they are likely to be very unreliable, so percentages should not be employed in those small series. I would call attention to the fact that this series is fairly large, therefore any criticism of this statistical paper can be eliminated.

I commend this paper to you for study because it upsets many of the ideas we have had with regard to the length of labor. He has called particular attention to the increase of the first stage. His most impressive table, of course, is his table regarding spontaneous rotation. I think that Calkins has this morning substantiated the conclusion of the great master, J. Whitridge Williams, who said: "I have learned to approach a case of occipitoposterior with entire equanimity."

DR. JOSEPH L. BAER, CHICAGO, ILL.—The diagnosis of occiput posterior has carried two implications for us on the staff at the Michael Reese Maternity: First, the possibility of a somewhat slower first stage; and, second, the possibility that nonrotation and lack of progress in the second stage would require intervention. Spontaneous delivery of persistent occiput posterior, usually unrecognized, has occurred in our maternity often enough through the years to keep us from being stampeded when the diagnosis is made.

The critical analysis presented by Calkins demonstrates two things: The efficiency of his organization which has enabled him to gather such a mass of reliable data; and the soundness of his conclusions which place the stamp of authority on our own policy. The negligible difference between occiput posterior and occiput anterior in length of first and second stages, demonstrated by the essayist, is among the most striking of his findings.

In my opinion occiput posterior should be treated as a normal position so long as labor progresses and the parturient and fetus show no evidence of damage. To this I add one reservation. After one hour of second stage with little or no progress, I prefer rotation and forceps application for the actual delivery of the unrotated head.

Manual rotation is safer than forceps rotation for the average operator, especially in the primipara. Whether manual or forceps rotation is undertaken, its ease and harmlessness are greatly enhanced by initial upward dislodgement of the impacted fetal head.

DR. CALKINS (closing).—Dr. Baer and I find ourselves in quite substantial agreement in that after an occiput posterior has been in the second stage of labor one hour without substantial progress, we believe in interference. I think he would also take that stand with occiput anterior, so there is really no disagreement. In these 2,400 cases I presented that rule was followed.

NEWER CONCEPTS OF BLOOD COAGULATION AND THE CONTROL OF HEMORRHAGE*

EDWARD A. SCHUMANN, M.D., F.A.C.S., PHILADELPHIA, PA.

A PRIME factor in the mechanism of its production and the control of hemorrhage is the element of coagulation time of the blood.

With hemophilia at one end of the scale and the recently described disease thrombophilia at the other, coagulation time is seen to play the chief role from causing continuous bleeding on the one hand, to the production of scattered thrombi in otherwise healthy individuals on the other.

In traumatic hemorrhage coagulation time is also an important element, although naturally not so dominant as in the bleedings due to an inherent variation in this phenomenon.

It has long been recognized that, especially in hemorrhage of the capillary or venous type, the generalized oozing from raw surfaces during surgical operations, uterine mucosal bleedings and so on, reduction of the clotting time is of great value and hence investigators have studied many substances with this end in view.

Horse serum, moccasin venom, cephalin, and many other agents have been used to shorten clotting time with more or less uniformity in their action.

Recently Arthur Steinberg (Ph.D.) and W. R. Brown (Ph.D.) have been working on the problem of blood coagulation and have presented their findings in a paper read before the American Physiological Society at its 1939 meeting and entitled "A New Concept Regarding the Mechanism of Clotting and the Control of Hemorrhage." The statements immediately following are largely taken from the article alluded to. Extracts have been prepared from certain plants which have been found to accelerate the rate of the coagulation of the blood markedly and rapidly. The best plant sources have been found to be shepherds' purse, wood sorrel, beets, oxalis, citrus fruits, alfalfa, etc. These extracts have been biologically assayed in rabbits and a unit has been devised which is defined as the minimum amount of material which will reduce the coagulation time of a five-pound rabbit 50 per cent fifteen minutes after an intravenous injection. The extracts were found to be nontoxic in rats, rabbits and guinea pigs, contained no alkaloids or proteins and could be administered intravenously or intramuscularly without ill effects.

Similar extracts were prepared from placenta, cord blood, spleen, liver, bile, etc., which also possessed marked hemostatic properties.

From these preparations Steinberg and Brown isolated colorless monoclinic crystals, having a melting point of 100° C. and which possessed most of the clotting power of the extract. These crystals were identified as oxalic acid. Solutions of pure commercial oxalic acid were prepared in the same concentration as present in the extract and were found to possess the same power to reduce coagulation time in the rabbit as the extracts themselves.

A titrametric test for oxalic acid in the blood was devised and normal values for human beings were established at 5.5 to 7.5 mg. per 100 c.c. and for rabbits at

*Read at the Sixty-Fourth Annual Meeting of the American Gynecological Society, White Sulphur Springs, W. Va., May 22 to 24, 1939.

amounts have been administered without any appreciable ill effects. The material is of value in hemorrhage of any type, but experience has shown that several modifications in administrative methods are necessary in certain types of bleeding.

In cases where hemorrhage is associated with increased permeability of the blood vessels as melena, the purpuric state, etc., the effect of koagamin is much enhanced if the patient be given massive doses of vitamin C for several days, preceding the exhibition of the coagulant in order to decrease the vessel permeability. When profound anemia is present, it is well to inject a donor with koagamin fifteen minutes before a blood transfusion, under which circumstances the maximum effect is obtained.

Koagamin has been extensively employed in the treatment of hemorrhage of various origins, hematemesis, bleeding gastric ulcers, jaundice, hemoptysis, hematuria, epistaxis, hemophilia, melena neonatorum and other forms of bleeding, with gratifying results.

I, naturally, have been especially interested in the use of this product in the management of hemorrhage arising from an obstetric and gynecologic service.

In hemorrhagic disease of the newborn, it has proved highly efficacious, an interesting demonstration having occurred in the obstetric division of the Philadelphia General Hospital. Identical twins were born, both suffering from hemorrhagic disease of the newborn; one baby was given mother's blood intramuscularly without benefit. The other received koagamin intravenously and intramuscularly, all evidence of hemorrhage ceasing within one-half hour. The first twin later was given the same preparation, after which it too stopped bleeding within a short time.

The use of this material has since become routine in all cases of melena neonatorum, arising in the services at Kensington and Chestnut Hill Hospitals, with excellent results.

In post-partum hemorrhage and in placenta previa, its action has been satisfactory, although more difficult to evaluate since bleeding of this type often ceases spontaneously. In a number of cases, we have observed that the bleeding of placenta previa diminished, even ceased, coincidentally with the sharp reduction of coagulation time brought about by koagamin. The action of this material can be well demonstrated if one has two plastic operations to perform during the same clinic. If one patient be given koagamin in the proper dose, fifteen minutes before operation, the other no special treatment, the difference in the bleeding of the operative field will be noteworthy. In the one case the dissection is almost dry, unless a spurting artery is cut, whereas in the other the usual venous ooze will be seen.

The question arises as to whether it is safe to use koagamin during the course of an operation, the fear being that subsequent relaxation may follow the wearing off of the effect of the drug. This has not been noted in our series of cases, because whenever koagamin is given during or im-

mediately after the course of an operation its use is continued for from twenty-four to forty-eight hours, after which much danger of hemorrhage has usually ceased. In uterine bleeding, either of the functional type or, more particularly, the bleeding from fibroid tumors of the uterus, koagamin exerts an active influence. In fibromas the hemorrhage usually ceased within twenty minutes after the intravenous injection of the drug and, while it may recur, the quantity of blood loss has been definitely much less after the injection than before. Hemorrhage of functional origin yields also to this preparation in rather dramatic fashion, although the theoretically correct treatment of the hyperplastic endometrium with antuitrin-S should not be neglected. After difficult pelvic enucleations, the oozing raw surfaces in the cul-de-sac which are not capable of being covered by peritoneum may be rendered quite bloodless by the use of koagamin.

A patient now under treatment presents an interesting demonstration. A woman of 48 years had a massive hemorrhage from the urinary bladder, sudden in onset and without previous symptoms. The hemorrhage was so alarming that the patient's physician washed out the bladder with a saline solution in the hope of removing blood and with the idea that the solution might terminate the hemorrhage. This proved unavailing and the patient was referred to Kensington Hospital for Women. Immediate blood transfusion was performed and then an attempt to visualize the bladder mucosa by the cystoscope was made and was unsuccessful, there being far too much active hemorrhage to utilize this instrument. Koagamin was administered, 3 c.c. intravenously and 2 c.c. intramuscularly every four hours thereafter. The bleeding continued for about two hours and was then reduced to a pinkish serous flow, but the patient complained of increasing vesicle pain and great tenesmus. Forty-eight hours later another attempt at cystoscopy proving abortive, the bladder was incised through the anterior vaginal wall with the idea of direct inspection of its interior. A huge, very firm blood clot with urinary crystallization beginning upon its surface was extruded from the bladder; the clot on examination was firm and tenacious and could be pulled apart only with difficulty. The bleeding did not recur and the patient is awaiting the subsidence of her acute cystitis before further investigation as to the cause.

The above scattered instances will serve to illustrate the uses of this new preparation on the gynecologic and obstetric services. Whether continued acquaintance with its properties will alter the convictions of the staff as to its efficacy in controlling hemorrhage cannot be stated, but it is true that at the present time the entire service is enthusiastic concerning it.

REFERENCE

Steinberg, A., and Brown, W. R.: *Am. J. Physiol.* 126: 638, 1939.

1814 SPRUCE STREET

DISCUSSION

DR. WILLIAM E. CALDWELL, NEW YORK, N. Y.—I am sure none of us is prepared at this time adequately to discuss the findings of Schumann and his co-workers. It is rather startling to find a drug which is frequently used for suicidal purposes, and which has so long been considered an anticoagulant rather than a coagulant, advocated in the control of bleeding.

Kenneth B. Olsen of the Department of Surgery, Presbyterian Hospital, who has been working on the problem of the coagulation of the blood and who had heard

Steinberg's paper at Toronto at the meeting of the Society of Experimental Medicine and Biology, has sent me the following letter which I would like to include in this discussion:

I believe that Schumann's statement that oxalic acid is the active principle of vitamin K is probably a misunderstanding as I know of nothing that would tend to prove this. Vitamin K is chiefly of use in the bleeding tendency that sometimes develops in obstructive jaundice, and there is some evidence that it is effective in hemorrhagic disease of the newborn. Oxalic acid on the other hand seems to have been effective in a large variety of cases. I had the privilege of hearing Steinberg's paper recently at Toronto, and he did not link vitamin K with oxalic acid.

There were several questions which I wanted to ask Steinberg, among them being the method used for determining the decrease in coagulation time. Presumably they used the venous coagulation time, and in my experience this is a very unsatisfactory and unreliable method. Patients with a prothrombin deficiency, as in some cases of obstructive jaundice, may bleed considerably and yet have a normal venous coagulation time. The converse of this is true in hemophilia. I should like to know the effect of oxalic acid on the prothrombin content of the blood and on other factors concerned in blood coagulation, especially calcium?

Clinical observations of bleeding patients are notoriously untrustworthy unless all of the facts are known. Postoperative hemorrhage or oozing is usually treated by a variety of mechanical measures in addition to blood transfusions, and if a coagulant is administered in addition to the above measures, it is difficult to assign hemostasis to any single measure. Fortunately most postoperative hemorrhages, unless due to a known cause or a pre-existing condition, will stop spontaneously. I should like to know what other measures were tried and in what manner they failed.

Excessive menstrual bleeding or intrauterine hemorrhage is also due to a variety of causes and I should like to know the details of the previous or concurrent measures that were used in the treatment of these bleeding cases?

Dr. Randolph West of this hospital has used an extract of shepherd's purse (a plant extract recommended by Steinberg and Brown) on a case of hemophilia, and it was without significant effect.

Steinberg also states that cord blood contains as high as 17 mg. per cent of oxalic acid by the method of Suzuki, yet so far as I have been able to ascertain, the coagulation of cord blood is essentially normal by the commoner methods. There is considerable evidence that a low prothrombin level exists in cord blood and that hemorrhagic disease of the newborn is due to a prothrombin deficiency. It seems paradoxical that oxalic acid should prevent bleeding in blood which already contains three times the normal oxalic acid content.

It would seem fairly simple to produce a bleeding tendency in animals by either the use of heparin or by producing obstructive jaundice, and it would be of great interest to know if the blood oxalic acid content was inversely proportional to the coagulation time. The reduction of the coagulation time by 50 per cent is not unusual after simple venipuncture if the venous coagulation time method is used as the limits of normal values in this test are quite wide.

Numerous reports are available concerning the toxicity of oxalic acid, as it is a material commonly used for suicide. The symptoms are gastrointestinal, consisting of vomiting, diarrhea, and cramps—and neuromuscular, consisting of twitching of the muscles, tetany, convulsions, coma, and death. Certainly the widespread use of this material should not be advised without more careful study of its pharmacologic character and definite advice as to the amounts which may safely be administered.

In conclusion, again, the proof of the pudding is in the eating. A very careful conservative man has advocated the use of oxalic acid in controlling bleeding. The many theoretical questions which come up must be answered in time and, in spite of Schumann's results, I would urge extreme conservatism in its universal use, until the many questions have been answered by the complete paper and independent research.

DR. SCHUMANN (closing).—I cannot answer these statements in the discussion read by Caldwell as many of them are obviously made without knowledge of the experimental facts which have been set forth in my paper and which are based on a large number of experiments.

With regard to the danger of oxalic acid, I may say that this drug has been given to something over 1,200 patients, often in repeated doses. Not only have no deleterious effects been observed, but we have not yet noted a single reaction of any sort. I therefore feel that the danger is negligible.

ELECTRICAL AND MECHANICAL ACTIVITY OF THE HUMAN NONPREGNANT UTERUS*

EDMUND JACOBSON, M.D., JULIUS E. LACKNER, M.D., AND
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(From the Laboratory for Clinical Physiology, Chicago; and from the Department of Gynecology and Obstetrics of Michael Reese Hospital)

THE human uterus has not yet been studied by the extremely sensitive methods now open to the electrophysiologist. Accordingly, we have sought to make an introductory survey in this field, limiting our efforts to the nonpregnant organ under normal and certain pathologic conditions. We have secured mechanical tracings simultaneously, as an aid to the first interpretation of the electrical records. This has required us to develop a particularly sensitive air recording system connected with a bag in the uterus filled only with air.

Contractions have been registered by mechanical contrivances by various workers including Schatz,¹ Knaus,^{2, 4} Moir⁵ and one of us (J. E. L.⁶⁻⁸). Contractions can also be registered by electrical methods as developed by one of us (E. J.) in 1930 for human skeletal muscle, even if the contraction is microscopic in extent. Limits of space preclude an historical account of the electrical studies on smooth muscle made by Matteucci,¹⁰ Fuchs,¹¹ Foà¹² and others. In later years uterine contraction voltages† have been studied in the guinea pig, cat, rat, and other mammals.¹³⁻²⁰

Contraction voltages in the human uterus have been studied by Theilhaber,²¹ Veit,²² Bode²³ and Falk and Nahon.²⁴ These studies may be regarded as introductory only, for in our opinion the electrodes have not been of suitable metal, nor have they been placed properly for reliable records, while the apparatus employed (the string galvanometer) is not sufficiently sensitive to obtain records from voltages present in many women.

METHODS AND PROCEDURE

1. *Electrical Instruments.*—For the present studies, two string galvanometers were available. The string tension on one (Sanborn) was set at 1 cm. per 3 millivolts; on the other (Cambridge) 1 cm. per 4 millivolts. Tension higher than in electrocardiography is employed in order to render the response to higher frequencies more accurate. With the tension as stated, the characteristic is flat up to about 200 cycles at least.

By means of a switchboard any one of three amplifiers could be thrown in circuit with either galvanometer. These assemblies have been described previously (Jacobson, 1930, 1931)^{25, 26} except for certain im-

*Presented at a meeting of the Chicago Gynecological Society, May 19, 1939.

The generous cooperation of the Bell Telephone Laboratories is again gratefully acknowledged.

†The customary term is "action-potentials." We propose instead "contraction voltages" for the potentials in electrodes in muscle tissue associated with contraction.

provements which cannot be outlined for lack of space. "Amplifier 1" is of the resistance-capacity type. Upon the application of a steady voltage to the input, the string deflection declines to zero in about four seconds. "Amplifier 2" and "Amplifier 3" are transformer coupled, capable of recording higher frequencies only: from about 30 to 4,000, they show a flat characteristic. In place of 1 cm. deflection per millivolt, they make it possible to secure, when needed, 1 cm. deflection per microvolt. The voltage sensitivity available is therefore one thousand times that of the string galvanometer alone. Any lesser sensitivity needed can be secured at will by a shunt (1-10,000 ohms) placed across the string terminals.

2. *Electrodes.*—In order to record uterine contraction potentials reliably, electrodes should penetrate into the uterine tissue. This secures not alone direct contact, but avoids potentials due to differential action of fluids in the uterine cavity or other space containing the electrodes. In addition, the uterine tissue acts as a thermostat, averting thermal potentials which otherwise prove confusing if delicate measurements of transient potentials are attempted.

Platinum-iridium wires, with points sharpened for penetration have been described previously (Jacobson, 1933).²⁷ The wire is pushed into the tissue for about 5 to 6 mm. or more. No wire is exposed, for what does not lie within the tissue is covered with insulating material.

The purpose of using such wire electrodes is to secure a record of potentials in them resultant from electrical pressures in a considerable portion of adjacent muscle fibers. (Concentric electrodes were used in one study only.) The following combinations of localities were employed: (A) *Two electrodes in the fundus musculature, a few millimeters apart* (Fig. 1, c). (B) *One electrode in the fundus musculature, with the other in the cervix* (Fig. 1, a or b). (C) *Both in the cervix.* In all instances the wires are inserted to the insulated hilt.

The electrode connected with the grid of the first tube in Amplifier 1 or with the inner part of the winding of the input transformer when either Amplifier 2 or Amplifier 3 is used is arbitrarily called "positive." This electrode is always the one inserted into the fundus musculature when the other is inserted into the cervix.

In addition, during certain studies on the uterus, simultaneous electrical records were taken with platinum-iridium wire electrodes inserted to the insulating hilt into the (skeletal muscle of the) abdominal wall.

3. *Mechanical Records.*—A deflated balloon was inserted into the fundus cavity for many tracings. This was conveniently assembled into the same device as carried the electrode which was inserted into the fundus musculature (Fig. 1, a). Flexible tubes provided passage of air currents from the inside of the balloon to the inside of a disc-shaped hollow container, the open face of which was covered with a sheet of Penrose rubber, after the pattern of a Marey tambour. This rubber was like that in the balloon. A tiny metal disc glued to the center of

the rubber facing carried a very fine hook, connected by a short length of inelastic fiber to a wheel which moved with a lever mounted on a shaft on jewel bearings, counteracted by a damping spring. This assembly (which can magnify about seventyfold) had been used for other purposes in previous studies (Jacobson,²⁸ 1930). The lever moves freely in the horizontal position, but its free terminal was bent vertically, so that its movements made a shadow on the photographic record.

By-pass tubes with stopcock arrangements made it possible to inflate the balloon after it was in the uterus, using an air syringe, while the pressure in the system could be tested with an oil manometer. As a rule, when used most sensitively, the pressure was approximately equal to a column of water 95 cm. in height.

Leakage of air was tested for carefully before the experiments. It was avoided in later tests, but not always in the earlier ones, some of which had to be discarded.

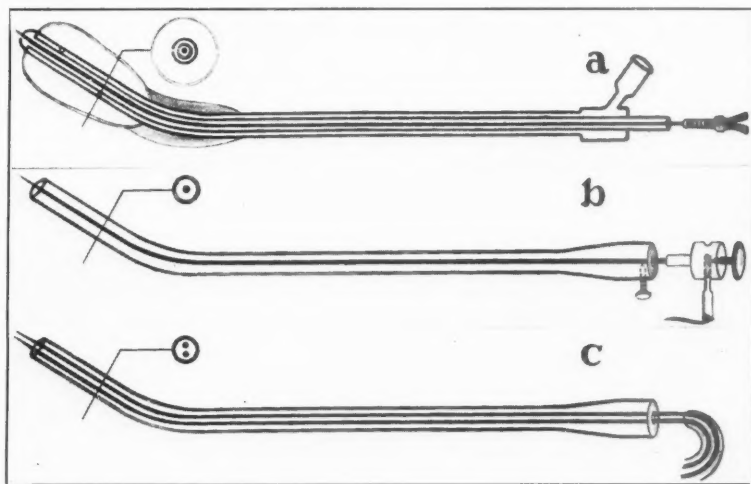


Fig. 1.—Catheters containing wire electrodes for insertion into the corpus uteri (a) with and (b, c) without a bag.

The platinum-iridium wires appearing in black in Fig. 1, *a* are freely movable and are completely insulated with bakelite varnish everywhere excepting at the tip. During insertion the wire or wires lie entirely within the containing sheath (metal in *a*, leather in *b* and *c*); but when the sheath makes contact with the inner wall of the fundus, the wire can be pushed out into the fore end of the corpus. The number of millimeters of protrusion is determined by the scale marked by a wire on the handle.

4. *Rooms.*—The laboratory is provided with a separate, shielded room for the patient and the couch on which she lies. Amplifiers and standardizing devices are concealed within the couch. Leads from the patient pass to wall plates connected with an elaborate switchboard in another room—the instrument room, containing the galvanometers. Similarly

the air tube passes from the patient to connections through the wall with the mechanical recording devices in the instrument room. In this manner, the patient is kept free from disturbance by the movement and speech of the operators.

5. In all, twenty-nine women have been studied. In planning an introductory survey, our aim was to secure something like a random sampling at various ages and at various times of the menstrual cycle in normal individuals as well as in some diseased conditions. We did not seek to make an exhaustive study of any one condition or of contractions at all of the stages of the menstrual cycle.

In Table I and Table II are presented pertinent data concerning these patients.

TABLE I

Total No. cases	29
Total No. experiments	34
Age variation	19 to 51
Parity (average)	2.2
Time of cycle	
First half (patients)	10
Second half	9
Menstruating	2
Irregular	5
Postmenopausal	1
Posthysterectomy	1
Post partum (6 weeks)	4

TABLE II

Present Complaints:	NO. OF PATIENTS
Vaginal discharge	9
Abdominal pain	8
Irregular menses	4
Menorrhagia	4
Backache	4
Premenstrual nervousness	4
Dysmenorrhea	1
Pruritus vulvae	1
Dyspareunia	1
Sterility	1
Abnormal Pelvic Findings:	
Retroverted uterus	4
Chronic endocervicitis	4
Chronic adnexitis	3
Fibroid uterus	2
Prolapsed ovary	1

RESULTS

For purposes of comparison with human records, tracings from the virgin uterus of a dog are shown in Fig. 2. Two fine platinum wire electrodes are inserted into the left horn of the exposed uterus. Operation had been performed previously by Roy Templeton. The wound had healed perfectly. No anesthetic was needed, for the dog evidently was not disturbed by the electrodes. Some of the spontaneous contractions were sufficiently large to be grossly visible before the electrodes were inserted, while others could not be seen, but were recorded clearly.

Quiescent periods often varied from about thirty seconds to nine minutes; the beginning of one is illustrated in the terminal portion of the tracing shown in Fig. 2, *a*. The first contraction would then appear, but relatively small, followed perhaps in two seconds by a second contraction, equally small or a little larger; then as if the mechanism had become started, successive contractions would come at briefer intervals, generally a small fraction of a second, and in stronger form. About thirty-one contractions appeared in one series; but the number varied considerably and the amplitude of the contraction in one series would differ considerably from that in another. It is convenient to classify and to present the illustrative data in women according to the locations of the electrodes.

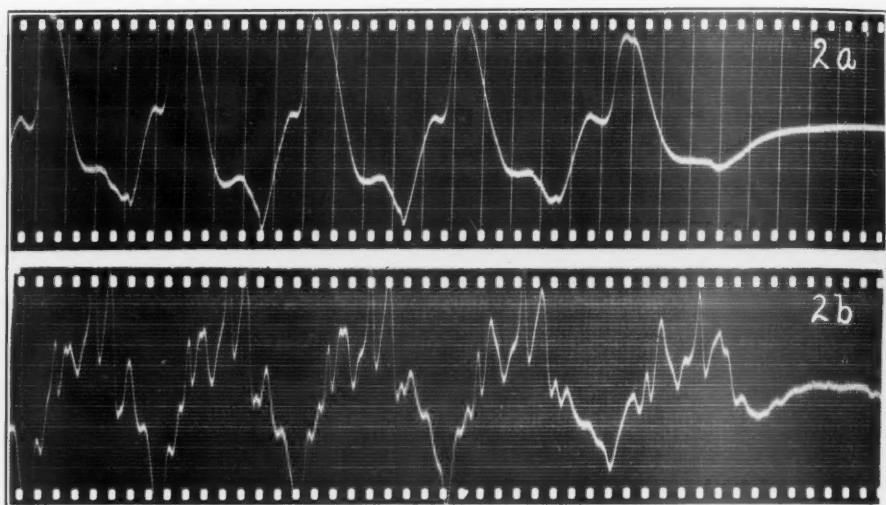


Fig. 2.—*a*, This photographic record of contraction voltages illustrates a period of regular recurrence at about 1 per second. Interval between vertical time lines = 0.2 second in this and in all subsequent figures. Read from left to right in all figures. 1 cm. = 0.8 millivolt. Amplifier 1. The control test, when a short-circuit exists across the input terminals of the amplifier, is a straight horizontal line. *b*, Contraction voltages at another time, 1 mm. = 4 microvolts (μ v.). When a short-circuit exists across the input terminals of the amplifier, the string is approximately quiet.

Uterograms, Type A.—Two electrodes in fundus tissue:

CASE 1.—D. B., aged 22 years, had been married six months. Menstruation was irregular; last period profuse, ended three days previously. Physical examination, including bimanual examination, was negative. Two platinum electrodes were inserted directly into the body of the uterus (Fig. 1, *c*). We present a recording with the string galvanometer direct (Fig. 3, *a*), with Amplifier 1 (Fig. 3, *b*).

In contrast with the nonpregnant dog mentioned above, quiescent periods do not exceed two seconds; they frequently last about 0.5 second. During control tests, with conditions identical, except that the tips of the electrodes have been withdrawn a few millimeters into the leather sheath, still lying within the uterine cavity, the results are negative, i.e., no deflection is shown by the galvanometer string (Fig. 3, *c*). The findings confirm the view that the human nonpregnant uterus undergoes spontaneous contractions, at least at times. The objection is answered that such contractions are perhaps due to a bag, acting as a stimulating foreign body within the

cavity, for here was no bag. It can be assumed that the fine short wires inserted do not stimulate contraction, for in skeletal muscle such wires have been used in hundreds of recordings in the absence of all contraction. Favoring this assumption also is the fact that in the dog's uterus some of the spontaneous contractions were readily visible before the two wires were inserted.

Evidently, then, with two wire electrodes in the fundus tissue of the human uterus, contraction voltages can be recorded. The curves are analogous to those secured when electrodes are inserted into the exposed uterus of the dog.

Uterograms, Type B.—One electrode in fundus tissue; the other in cervix (anterior or posterior lip). Bag in cavity of corpus uteri.

CASE 2.—S. H., aged 22 years, para i; gravida i. Menses: Regular twenty-eight-day cycle; last period four days ago. Present complaint: Vaginal discharge. Cervix cauterized six weeks previously.

Since the corpus is richer in muscle tissue, electrical pressure changes accompanying contractions will be greater than in the cervix. In common terms, the electrode ("negative") in the cervix tissue will be relatively "indifferent."

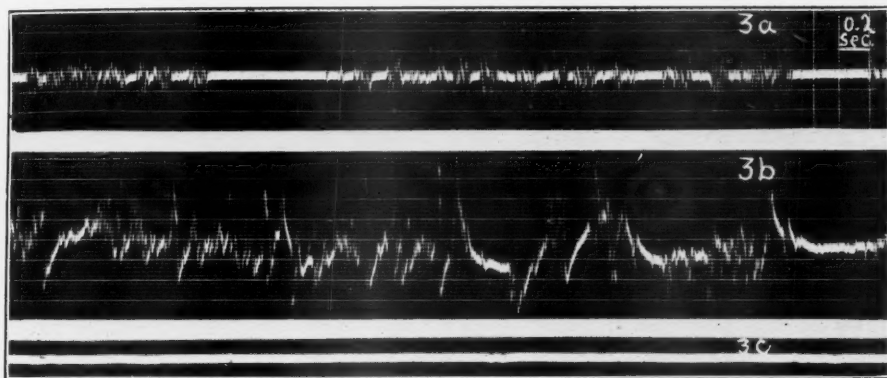


Fig. 3.—*a.* (Patient D. B.) Contraction voltages in human uterus recorded with string galvanometer alone. Both wire electrodes in fundus tissues. 1 cm. = 1 millivolt. *b.* Contraction voltages in same uterus, somewhat later, recorded with Amplifier 1. Both wire electrodes in fundus tissue. 1 cm. = 0.5 millivolt. (Deflection of string is upward when potential on grid lead becomes positive.) *c.* Control test, showing negative results when the conditions remain the same as for Fig. 3, *b*, except that wires have been withdrawn from the fundus tissue but remain in the sheath lying undisturbed in the uterine cavity. The tips of the leads are in contact, effecting a short-circuit.

Tonus in smooth muscle, so far as we know, has not heretofore been successfully measured in the intact animal. In skeletal muscle this has been accomplished by one of us using the present equipment.^{29, 30} In Fig. 4, *a* (patient S. H.), we present an example (of which we have many) of the first electrical recording of tonus in smooth muscle; in this instance, the human uterus. Similar examples were secured (in 1935) with the dog's uterus (not published heretofore).

Fig. 4, *a* and *c* show mild but steady tonic contraction before pituitrin was administered (compare respectively with controls, Fig. 4, *b* and *d*). Shortly after the hypodermic administration of one ampoule of surgical pituitrin, contraction voltages increased markedly (Fig. 4, *e*); they now could be seen clearly even with the string galvanometer alone (not figured).

Contraction voltages are here enhanced after pituitrin, illustrating that the present electrical methods can be most useful in the study of oxytocic and other influences. In this one instance the mechanical system fails to show a clear-cut response after pituitrin, apparently not being sufficiently sensitive. This was improved during later studies, partly by increasing the air pressure in the system.

CASE 3.—R. A., aged 22 years, para ii, gravida ii. Menses: Regular twenty-eight-day cycle, last period 10 days ago. Complaint: Leucorrheal discharge. Physical examination negative, excepting endocervicitis.

Fig. 5, *a* illustrates that at times the electrical recording, as secured by present methods, manifests a striking parallelism with the pneumatic tracing. At times the two tracings are actually superimposed! That this can happen in such detail is remarkable, because the two systems are so different in operation. Without doubt, artifacts can be ruled out: no mechanical vibration such as jumping or stamping on the floor can cause any parallelism. (The floor, in fact, is approximately vibration-proof; for it is constructed of double thickness and strength to support safety-deposit vaults.)

Probably it is fitting to call Fig. 5, *a* a "tonus tracing"; for the picture taken very soon thereafter, using Amplifier 2 for higher frequencies only, reveals this character clearly. (Obviously, parallel tracings like those in Fig. 5, *a* could not be secured if only higher frequencies are recorded as in Fig. 5, *b*).

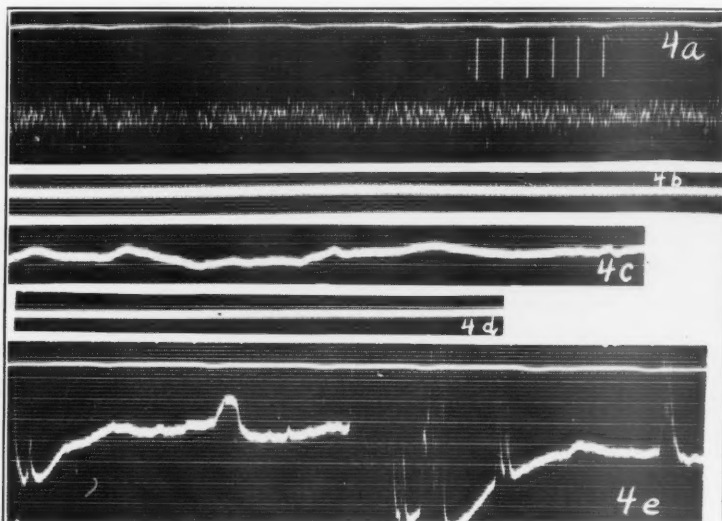


Fig. 4.—*a*. (Patient S. H.) Tonus in the human uterus, recorded electrically (lower tracing). One electrode in corpus, the other in cervix tissue (Type B, electroutero-gram). The pneumatic record (above) fails to show tonus clearly, for the tracing is almost a straight line, broken only by slight, concave pulse marks. 3.5 mm. = 1 microvolt. (Higher frequency record, made with Amplifier 2.) *b*. Control test. Conditions same as for Fig. 4, *a*, except that a key closes a circuit across the input terminals of the amplifier. Hereinafter this will be called short-circuit test. *c*. Recording simultaneously with that in Fig. 4, *a*, but secured with Amplifier 1. The voltage sensitivity here is insufficient to portray a clear, electrical record. 1 cm. = 1.5 millivolts. Deflection is upward when electrode in corpus tissue becomes electro-negative. *d*. Short-circuit test. Conditions same as for *c*. *e*. Approximately 1.5 minutes after hypodermic administration of pituitrin. Conditions same as for *c*. (Short-circuit value shown in *d*.) Contraction potentials marked (lower tracing), while pneumatic system (upper tracing) fails to display uterine contractions.

Following the hypodermic injection of 1 ampoule of surgical pituitrin, slight positive effects can be distinguished in the electrical record, as shown in Fig. 5, *c*, apparently as early as after only fifty-second interval. While the pneumatogram shows a continued rise in this figure, it is no greater than some others seen during a control period prior to the administration of the extract. The effect after the administration of pituitrin in this instance failed to become marked during a seven-minute period of observation.

CASE 4.—W. R., aged 24 years, para iii, gravida iii, married seven years. Menses: Twenty-eight- to thirty-five-day cycle, lasting ten days. Complaint: Premenstrual nervousness, beginning ten to fourteen days before the period. Pain in the lower

abdomen bilaterally passing to the back and legs intermittently since last delivery. Previous surgery: Appendectomy, perineorrhaphy. Physical examination: Uterus movable, retroverted; corrected by pessary.

Records of contraction of this patient's uterus were secured on the first occasion near the onset of her premenstrual tenseness. This was three weeks after her previous period but two weeks before the following one. The uterus showed marked contractions, as shown synchronously with the electrical and mechanical recording systems. Simultaneously, records were taken of contraction voltages in the abdominal musculature, which indicated that she was in a generally tense state at the time of measurement. While at first their magnitude was often on the order of 1 microvolt, after six minutes there was a marked increase of potentials on the order of six microvolts and after about another five minutes, the magnitude increased to peak microvoltages on the order of about 12.

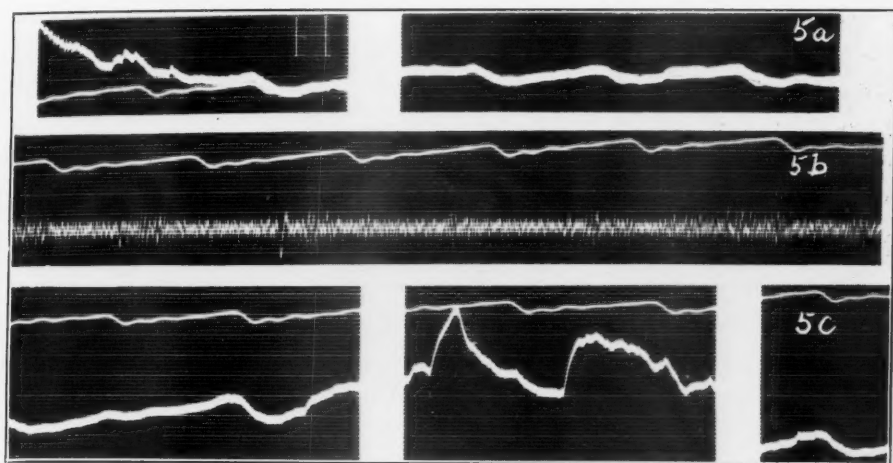


Fig. 5.—*a*. (Patient R. A.) Photographic tracings from contraction voltages (thicker line, Type B electroutero-gram) and from bag in uterine cavity. Approximate coincidence of these tracings is shown in the latter portion of the photograph, which is quite unusual. Note the recording of arterial pulsation simultaneously in both records. An interval of about seventeen seconds elapses (white space) between the two photographs in *a*. 1 cm. = 5 millivolts. Deflection is upward when electrode in corpus tissue becomes electronegative. The control test upon short circuit is practically a straight line, as shown in *c*. *b*, Tonus tracing and mechanogram before pituitrin (Amplifier 2). *c*, Compare with *a*. Effects of pituitrin, administered hypodermically about twenty-five seconds before this recording was begun, become noticeable after a total increase of fifty seconds, for increased contraction voltages appear where indicated by the arrow. Upward deflection of electrical curve (the thicker line), signifies potential in lead in fundus is negative. Upward deflection of mechanogram indicates uterine contraction, which here is not very marked. 1 cm. = 5 millivolts. In the double recording shown in *c*, the electrical tracing appears to be the more sensitive indicator; for the mechanogram, although rising here, does not show much change following the administration of pituitrin. A positive result is shown on the electrical tracing as early as (approximately) forty-five seconds after the administration.

The second recording was made during the following month, twenty-one days after the onset of the last menstrual period. Progesterone had been administered two days previously (2 rabbit units intramuscularly). Both electrical and mechanical records reveal that the uterus was then relatively quiet. Nevertheless the patient's complaints were not diminished. That the patient was in a generally tense condition was suggested by the records from her abdominal muscles which showed microvoltages comparable with the larger ones recorded on the former occasion.

In this study, it is shown that the condition of premenstrual nervousness can be recorded objectively. Possibly the progesterone was responsible for the relatively quiet state of the uterus on the second oc-

easion; but the extract failed to quiet the patient's neuromuscular tensions, as tested in the abdominal musculature, and failed to relieve her complaints.

CASE 5.—H. M., aged 31 years, para i, gravida ii. Menses: Regular, thirty-day cycle. Menstruating now, without pain. Previous surgery: Appendectomy, perineorrhaphy. Complaint: Sterility since miscarriage one and one-half years previously. Physical examination: Negative.

Recordings, both electrical and mechanical, indicate very marked uterine activity. One cycle, for example, lasting about twenty seconds, shows a microvoltage greatly exceeding 300. The uterine activity was present while the speculum and volsellum were in place but was equally marked after these instruments were removed completely.

These records illustrate that very marked uterine contractions sometimes take place without pain; in this instance they occur during menstruation.

CASE 6.—N. I., aged 51 years. Climacteric began four years ago, but a little bleeding at menstrual periods has persisted. Physical examination: Small atrophic corpus; normal cervix.

Tonus records are secured with this patient, resembling those shown in Fig. 4, *a*, but of higher microvoltage. The peak microvoltage is on the order of 8.0. No bag is inserted. When a physician (Dr. L.) enters the room and carries on prolonged discussion with her, the contraction voltages increase markedly, at times on the order of 18 microvolts.

This illustrates electrical records of tonic uterine contraction during the late menopausal period and their augmentation during conversation about matters of moment (probably emotional stimulation).

CASE 7.—W. R., aged 37 years, para ii, gravida iii. Last menstrual period seven days previously. Menses: twenty-eight- to thirty-day cycle; duration five to seven days with moderate flow but pain on third day. Symptoms: Clots in menses, discharge, pain in right lower quadrant. Previous surgery: None. Physical examination: Suggests possible fibroid uterus.

The uterograms, both electrical and mechanical, show marked activity. Following the intramuscular administration of 3 c.c. of corpus luteum (H.W.D.), diminished activity is indicated for the first time on both systems simultaneously after about forty-five to sixty seconds (Fig. 6). Control tests were performed subsequently by withdrawing the electrode from the fundus tissue but leaving it in the sheath with negative results, for the string was quiet.

In this instance, information concerning the reaction time of the hormone was afforded simultaneously by the two systems of recording.

CASE 8.—C. F., aged 35 years, para ii, gravida ii, six weeks post partum. Not nursing.

Both mechanical and electrical tracings show very marked uterine activity. Following the intramuscular administration of 3 c.c. of aqueous corpus luteum extract, a distinct diminution in the contraction voltages is discernible after about one minute. On the other hand, a diminution of contraction is not clearly discernible in the mechanical records until after about four minutes. A complete quieting fails to occur, as shown by either type of record.

For a control test, the wires were withdrawn a few millimeters, retracting the points from contact in the uterine tissues, while permitting them to remain within the sheath. The bag was left in place. The character of the voltages then secured in no way resembled what was seen previously, but evidently was due to liquid between the points, constituting a high impedance liquid contact. Following the experiment, the bag was removed and reinflated. A 20-minute test demonstrated the absence of any leak.

This study suggests that electrical recording, if sufficiently sensitive, is the procedure of choice to assay the reaction time of the effect of hormone and drugs on uterine activity.

Uterograms: Type C.—Both electrodes in cervical tissue.

CASE 9.—S. V., aged 21 years, para i, gravida i. Menses: Regular, twenty-eight-day cycle, three days' duration, moderate, severe cramping pain. Last menstrual period nineteen days previously. Previous surgery: Appendectomy. Present complaint (two weeks' duration): Lumbar backache, vaginal discharge, pruritus vulvae.

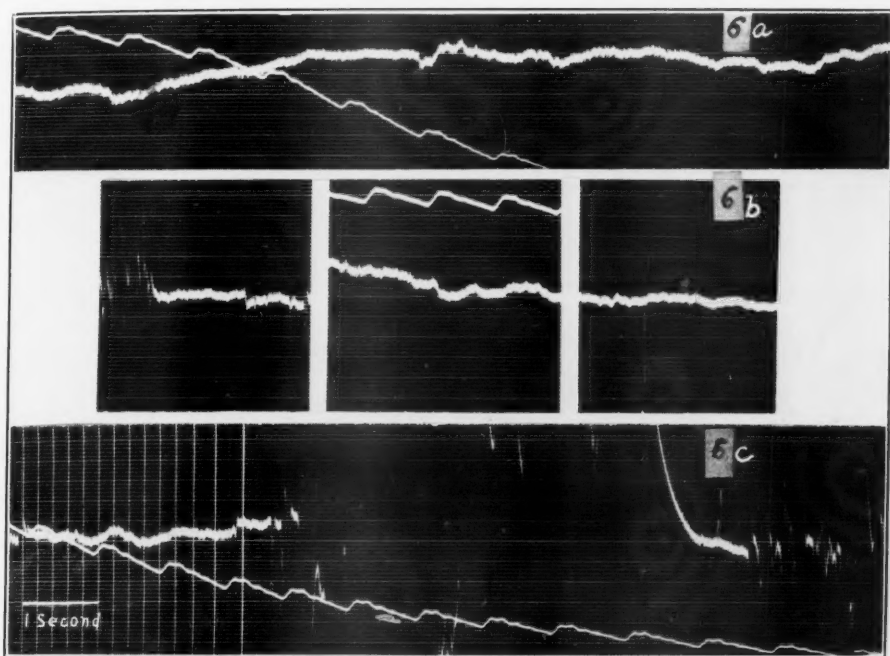


Fig. 6.—*a.* (Patient W. R.) Beginning about forty-five seconds or a little more after the intramuscular injection of an aqueous solution of corpus luteum extract, the uterus seems to be relaxing for a prolonged period. At this moment, the pneumatogram (thinner tracing) shows a sharp fall, passing off the photograph and remaining off or approximately so for the following one and one-half minutes; while the electrogram (thicker tracing) continues relatively quiet during the same period, aside from slight undulations, which probably indicate the persistence of moderate tonus. Type B electroutero-gram. 1 cm. = 65 microvolts. *b.* Control test about one minute prior to the administration of the hormone. Three frames are shown, each of which represents approximately three seconds of recording, while each of the two intervals or white spaces represents seventeen seconds. In the first frame, action-potentials are seen at the outset, but the pneumatogram is off the film on the contraction side, reappearing in the second frame. *c.* Another control test, beginning about one and one-half minutes prior to that shown in *b.* While the pneumatic tracing shows a decline, in the direction of relaxation, the voltage recordings are so marked as to pass off the film. Previous declines of the pneumatogram, like that shown here, likewise showed simultaneous marked action-potentials, in contrast with their absence in *a.*

At a time when the patient stated that she was having "uterine cramps," both mechanical and electrical tracings proved to be practically quiet. A simple intra-uterine bag was used for this mechanical recording. Following the administration of 1 ampoule of surgical pituitrin, the electrical record is the first to show changes, which become distinct after about three and one-half minutes. A distinct rise is seen in the mechanical tracing only after an additional eighty seconds. As seen on the mechanical record, a complete cycle of moderate contraction following this point

requires one to two minutes. After about five minutes a marked and sustained tonic increase occurs which is sustained for about five minutes, followed by a fall in tonus and return of smaller contraction periods. The effects of pituitrin are noticed considerably earlier in the electrical than in the mechanical tracing. Clearer information regarding the length of individual contractions and the sustained tonus on which these contractions are superimposed is secured from the pneumatograms.

CASE 10.—K. M., aged 32 years, para iii, gravida iv. Menses: Regular, twenty-eight-day cycle, four days' duration, marked by flushes, backache and irritability for seven to ten days preceding the menstrual period. Next menstrual period expected in eight days. Physical examination: Uterus retroverted, corrected by pessary. Present complaint: Nervousness for ten days before menstrual period.

Electroutero-grams, Type C, indicated a continued presence of steady tonus much greater at some times than at others. Tonus is present with the speculum in place, but also after it has been removed. About two and one-half minutes after the administration of pituitrin, a fivefold increase in microvoltage took place (as measured in the electrodes, using Amplifier 2). The change was from about 3 to 15 microvolts (maximum peaks), Fig. 7.

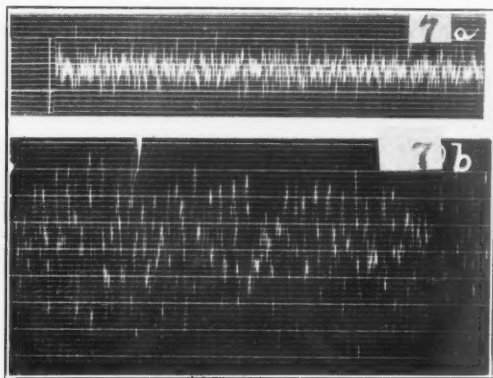


Fig. 7.—*a.* (Patient K. M.) Type C electroutero-gram. Tonus recording in uterus during premenstrual nervousness before the administration of pituitrin. 3.5 mm. = 1 microvolt. *b.* Same: Two and one-half minutes after the administration of pituitrin. The control test (not shown) is of the same character as *a*, *b*.

In this instance, the tonus change following the administration of pituitrin was conveniently measurable in the electrical record (Amplifier 2). This was not true in all instances studied, for in one instance, where the mechanical record showed increased contraction, the tonus change was not shown in the electrical record made during the height of contraction.

A second recording with this patient was made about six months later on the twenty-third day of the twenty-eight-day cycle. She stated that this was on the second day of her premenstrual nervousness. Very marked contraction voltages (passing off the photographic record, much exceeding 200 microvolts and lasting from about two to twenty seconds) occur after intervals of relative quiet varying from about four to fourteen seconds. Following the subcutaneous administration of 3 c.c. of aqueous solution of corpus luteum extract, the electrical record shows quieting results which are distinct somewhat after one minute. The quiet interval now persists for sixteen seconds, followed by a contraction voltage lasting about three and one-half seconds, succeeded by a quiet interval of forty-four seconds. Meanwhile the mechanical record fails to give clear information.

Abdominal contraction voltages persist throughout on the order of 1-2 microvolts, showing no change after administration of the extract.

CASE 11.—T. E., aged forty-two years, para iv, gravida v. Two years previously: Subtotal hysterectomy. Present complaint: Dizzy spells and leucorrhea. Physical examination: Negative except endocervicitis in cervical stump.

The recording is of interest as showing that with both leads in the cervix, contraction voltages of active type can be registered. This indicates that sufficient muscle tissue remains to afford such responses or that the currents are conducted from the uterine musculature.

CONCLUSIONS

Decreased tonus and diminished contraction cycles in the nonpregnant uterus were seen following the intramuscular injection of an aqueous extract of corpus luteum. It is important to distinguish the interval at which relaxation begins to appear from the interval at which relaxation becomes for the first time complete, or as nearly so as is effected following the administration of the principle: We need to distinguish *beginning-relaxation time* from *complete-relaxation time*. If relaxation fails to become complete, and some contraction persists, it can be called partial-relaxation time. Recognizing these distinctions, we report instances where the beginning-relaxation time following the intramuscular administration of an aqueous solution of corpus luteum extract seemed detectable in so short a time as one minute. Since previous investigators (using no very sensitive indicators) report no such brief intervals, these results will need to be confirmed, since our studies were too few in number to warrant a conclusion on this point. It is perhaps pertinent that even much briefer contraction and relaxation times have been reported by Bender following the intravenous administration of physiologic extracts.³¹

For the study of premenstrual nervousness, the present methods afford means to secure objective records not alone of the uterine contractions or contraction voltages but also of the patient's nervousness (neuromuscular state). In this manner we are able to substitute for the patient's subjective or "psychic" complaints, a set of objective measurements.

In recapitulation, we conclude:

1. Activity of the human uterus can be successfully studied with the string galvanometer (or the oscillograph) plus amplifiers capable of measuring low voltages.
2. Physiologic studies of uterine activity can be made more completely if, in addition to the electrical measurements, mechanograms are made as well. Photographic tracings by electrical methods may show a striking correspondence or even parallelism with the mechanical tracings, but this depends upon what type of amplifier is employed.
3. Uterine tonus has been electrically measured in the present studies for the first time.
4. The effects of certain hormones and other agents on the uterus can be successfully detected by employing both mechanical and electrical measurements, each method supplementing the other. Following the intramuscular administration of an aqueous solution of corpus luteum extract, or the hypodermic administration of pituitrin, a relaxing or oxytocic effect (respectively) was detected in so short a time as one

minute. Since previous investigators generally report no such brief intervals of response, these results will need to be confirmed in this respect.

5. For the definite determination of special conditions, such as premenstrual nervousness, objective methods of recording are presented. By the use of such objective methods, conclusions about the patient's state and the effects of hormones and other preparations can be achieved with greater probability.

6. The most convenient method for electrical recording and the one with least discomfort to the subject results from insertion of both electrodes into the lips of the cervix. For many studies, insertion of a bag can be omitted altogether.

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DISCUSSION

DR. WILLIAM DIECKMANN.—The authors are to be congratulated for developing a new method of investigating uterine motility. This method requires no intrauterine manipulation and is applicable to uteri of any size. These studies should eventually give us information as to the cause of dysmenorrhea, the onset of labor, and the cause of uterine inertia. The rapid response to pituitrin and progesterone is unusual and raises the question as to whether the response is the result of a drug action instead of hormone.

DR. JACOBSON (closing).—Dr. Dieckmann has commented upon the importance of a method to determine accurately the time when progesterone, adrenalin, pituitrin or some other extract or hormone first takes effect. To determine the time for the onset of effect of any particular extract would, of course, require a statistical study on many patients with frequent repetitions in each individual. This we have not done, but we have obtained sufficient data to introduce the problem and have shown how it can be solved. Accordingly, the aspect of our work which regards reaction and relaxation times of the uterus following the injections of various extracts or hormones will need to be confirmed.

During the April meeting of the American Physiological Society, Bender* re-

*Bender, M. B.: Proc. Am. Physiol. Soc., April 26, 1939.

ported on the time of action of acetylcholine and of adrenalin when injected intravenously in the cat and monkey. Six seconds was the interval observed in the cat before the contraction of the denervated facial muscles. Fifteen seconds later a pronounced dilatation of the denervated pupil took place. Six seconds was the interval in the monkey before dilatation of the sympathectomized pupil showed the effect of adrenalin. Such brief times as Bender observed for the action of these agents when injected intravenously, while in no sense confirming our results in connection with the uterus, nevertheless harmonize with our present reports of very brief reaction and relaxation times of the uterus, following the administration of various extracts.

STUDIES IN ARTIFICIAL OVULATION WITH THE HORMONE OF PREGNANT MARES' SERUM*

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THE problem of sterility and infertility is a complex one, and its solution extends beyond mere conversation, explanation, and encouragement. The ultimate desideratum, fundamentally, in any given case should be to ascertain, if possible, which of the basic requisites for a successful fruition is at fault. Is it one of defective germ plasm, ovulation, or spermatogenesis; is it one due to some impediment of the passage of the gametes to the locale of fertilization; or, is it one due to an improper habitat for nidation or implantation, or one due to a combination of several, or all, of the aforementioned factors?

It is with the ovulatory factor that we are concerned in this communication.

When one considers the short span of life of the supposed "normal active liberated ovum" (for up to the present time we actually have no method of evaluating their normalcy), which today is practically certain to be less than twenty-four hours; and when one considers that the ovum is fertilizable for a still shorter time, the question of ovulation becomes of utmost importance. What is the time of ovulation in a given menstrual cycle, and in the cycle that follows? Does ovulation accompany every menstrual cycle?

From the data collected by Dickinson¹ and by Hartman,² and from our own investigation, the actual determination of the time of ovulation in the human being still remains a moot question. Of the many methods that have been used to ascertain the actual phenomenon of ovulation, none has been very definite as to its exact time in a given cycle. It is our impression, however, that ovulation in the human being occurs but once a month, and that conception is possible for only a few days in a menstrual cycle. This makes pregnancy in the human being much more of a hit and miss affair than in many animals, particularly those that have a definite estrus cycle.

In women, ovulation is ordinarily spontaneous, occurring in the absence of copulation, whereas in the rabbit, the cat, and the ferret,

*Presented at a meeting of the Brooklyn Gynecological Society, April 14, 1939.

ovulation is normally induced only by copulation. In normal rabbits, a nervous stimulation of the pituitary occurs on mating, producing the liberation of those hormones that cause ovulation.³ This usually occurs from about ten to twelve hours after copulation. This timed phenomenon in the rabbit makes this animal very useful in the experimentation for the determination of early ovulation.

The maturation of the Graafian follicle, the expulsion of the egg, and the formation of the corpus luteum are all induced by the correct admixture of the gonadotropic hormones of the anterior pituitary. Any disturbance of this intricate and delicate mechanism will cause an imbalance of these hormones with the consequent sequelae to the organs of reception, the ovaries, with resultant menstrual disturbance.

In 1927, Aschheim and Zondek,⁴ Smith and Engle,⁵ demonstrated the interrelationship of the anterior pituitary and the gonads. Moore and Price⁶ have presented a most complete and convincing evidence of the existence of this reciprocal relationship. The gonads are dependent upon the hormone of the anterior pituitary for a normal gametogenic output. Conversely, the gonads exert a controlling influence upon the anterior pituitary. Therefore, unusual activity of the gonadotropic hormones of the anterior pituitary may overstimulate the gonads. Conversely, the removal of a gonad may release its inhibitory factor on the gonadotropic hormone of the anterior pituitary.

Fevold and Hisaw,⁷ and Wallen-Lawrence,⁸ have reported the separation of both a true follicular-stimulating hormone, and an exclusively luteinizing factor from the pituitary tissues, while Foster and Fevold⁹ have demonstrated the interrelationship of various gonadotropic hormones to follicular development, and ovulation in the juvenile rabbit.

The gonadotropic hormones can be demonstrated to be present and can be extracted from many different sources, such as the tissues of the anterior pituitary body, from the blood and urine of pregnant women, from human placenta, from urine of the castrate and menopausal woman, and from the blood serum of pregnant mares. These specific substances derived from different sources exhibit certain specie differences, some of the most important of which are as follows:

1. Widespread follicle maturation¹⁰ is obtained in the infantile mouse, rabbit, rat, *Macacus rhesus* monkey with the extracts of the anterior pituitary, castrate and menopausal urine, and pregnant mares' serum. The action of the hormone of pregnancy urine, however, is limited, in that few follicles develop which do not ovulate, but become hemorrhagic, or form corpora lutea with imprisoned ova. This is the basis for the Aschheim-Zondek test.

2. Follicular development in the ovaries of the hypophysectomized rats¹¹ is induced by the administration of the hormones extracted from the anterior pituitary, castrate and menopausal urine, and from the pregnant mares' serum, but not by the hormone extracted from pregnancy urine.

3. The extract of the anterior pituitary¹² and pregnant mares' serum causes the growth of the testes of the infantile rooster, and distinct growth of the comb, which the hormone from pregnancy urine does not do.

Leonard and Smith¹³ found that pregnancy urine by itself will not produce maturation of the follicles, ovulation, and corpora lutea formation unless complemented by the gonadotropic factor in the urine of the castrates, of the menopausal, or the extract of the anterior pituitary.

Hamblen and others¹⁴ have reported that no evidence exists that the gonadotropes derived from pregnancy urine, placenta or the anterior lobe of the pituitary, when

employed singly or together, were capable of inducing ovulation or the formation of corpora lutea in the human being with estrogenic bleeding, even when given in huge doses.

It has been shown by Cole and Hart,¹⁵ and by Zondek,¹⁶ in 1930, that the serum of pregnant mares contains a gonadotropic-stimulating factor that causes ovarian stimulation such as described above, without further addition of a complementary factor.

Cole and Hart found that the gonadotropic hormone appears in the blood serum of the pregnant mare between the thirty-seventh and forty-second days of pregnancy, reaches a maximum between the fiftieth and eightieth days, and thereafter decreases and disappears between the one hundred and thirtieth and one hundred and eightieth days.

Zondek, in 1930, demonstrated that the hormone is excreted in the urine in only minute quantities. Glud and others¹⁷ confirmed Cole and Hart's findings. Cole and Saunders¹⁸ also showed that it disappears from the blood stream at the time that the greatest concentration of the follicular hormone appears in the urine.

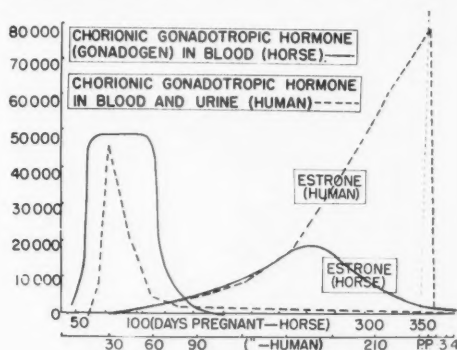


Chart 1.—Graph showing the concentration of the hormones in pregnant mares' serum and in the pregnant human serum and urine. (Modified from Cole and Saunders.)

In human pregnancy, on the other hand, the gonadotropic hormone can be demonstrated to exist both in the blood serum and in the urine. Both of these have been shown by others¹⁹ and by us³⁶ to be secreted and excreted with characteristic concentration for the normal.

In the pregnant mare, the gonadotropic hormone is found in the plasma, endometrium, chorion, and maternal pituitary.²⁰ It is not readily excreted by the kidneys in the mare,¹⁵ rat, monkey,^{10a} castrated rabbit, and gelding.²¹ It is not stored in the uterus, spleen, lungs, kidneys, and liver, and since the rate of disappearance is the same in the castrate as in the noncastrate rabbit,²¹ it is, hence, impossible, that the gonads play a significant role in its destruction.

In the human pregnant individual it is well known that prolactin passes the kidneys with ease. The concentration of the hormone in the blood serum fairly well agrees with that in the urine. Anterior pituitary-like hormone has been shown to be excreted in the urine of the rabbit,²² rats, and monkeys,^{10a} after the animals have been intravenously injected with the hormone of pregnancy urine. The same has been demonstrated in the nonpregnant woman who had been transfused from a pregnant woman.²³

Due to this property of the hormone of pregnant mares' serum, of remaining in the blood stream until it is destroyed, and not being ex-

creted in the urine, it allows its action on the gonads to approximate more closely a continuous one, than does that of the readily excreted anterior pituitary-like hormone.

We had injected, intravenously, 200 units of the hormone of pregnant mares' serum, in one single dose, to each of two amenorrheic cases, respectively of $6\frac{1}{2}$ and 2 years' duration, both of whom had negative estrin and prolan in the blood and urine before the administration of this hormone. We had not recovered any of the hormone as such in the urine after eighteen hours to five days, although concentrations of diminishing amounts were found in the blood serum taken daily over the same period. Complete data of these findings will be published in a later communication.

In general, the biologic effects produced by the hormone of pregnant mares' serum when injected into animals are more in the nature of a physiologic response than that produced by the hormone of the pregnancy urine. In this respect, the gonadotropic-stimulating action of the pregnant mares' serum more closely resembles the gonadotropic effects produced by the animals' own hypophysis. It was found that the injection of the hormone of pregnant mares' serum in young ewes produced ovulation during an anestrus season. A second dosage given seventeen days later resulted in a second ovulation with estrus, resulting in pregnancy when the ewes were mated.²⁴ Similarly, young sows when injected with the hormone of pregnant mares' serum produced ovulation at estrus, and pregnancy followed mating. Cows receiving large doses showed greatly enlarged ovaries when autopsied six days later.²⁵

Experiments on the stallion, bull and bear indicate that this hormone increases the activity of the Leydig cells of the testes resulting in enlargement of the seminal vesicles and prostate.²⁶ We have found this to be of help, clinically, in cases of oligospermia and necrospermia, increasing the number of motile sperm, in several instances 100 per cent, by the administration of the hormone of pregnant mares' serum in 10 U* doses every other day intramuscularly.

Follicular stimulation and development of the secondary sex characteristics with reddening of the skin areas can be produced in the immature rhesus monkey by the administration of this hormone.²⁷ Hartman²⁸ has been able to produce ovulation in anovulatory adult monkeys. He was able to demonstrate the ovum thus produced with the hormone of pregnant mares' serum.

We have found that follicular formation can be visualized two hours after the intravenous injection of 2 U of the hormone of pregnant mares' serum, administered to an immature rabbit weighing $2\frac{3}{4}$ pounds, ovulation taking place as early as eight hours. In the immature *Macacus rhesus* monkey, weighing $7\frac{1}{2}$ pounds, after daily intramuscular injection of 5 U of this hormone, we have found on the third day, reddened external genitalia and enlarged nipples, and on laparotomy on the seventh day, enlargement of the ovaries to about 8 times their original size, with diffuse follicular stimulation and hemorrhages.

*U, the Cartland and Nelson Unit—the minimum total dose of hormone which, administered to twenty-one- to twenty-three-day-old rats, weighing 35 to 45 gm., in three equal subcutaneous injections at daily intervals, will produce at autopsy, ninety-six hours after the first injection, a mean ovarian weight of 65 mg. which is four to five times that of the controls.

Siegmund,²⁹ Moricard and Saulnier,³⁰ and Watson and others,³¹ were able to stimulate follicular development in women with the hormone of pregnant mares' serum, but could not show ovulation in any of their cases. In 1937, Davis and Koff,³² were able to demonstrate by laparotomy that ovulation could be produced by the intravenous administration of this hormone. This, combined with our growing conviction that many cases of sterility in women, who were bleeding cyclicly, were due to failure of ovulation, prompted us to investigate this new gonadotropic substance.

METHODS

1. An attempt was made to corroborate the work of Davis and Koff.
2. Where ovarian response could not be studied by laparotomy, it was possible to do so by the endometrial response using repeated suction biopsies of the endometrium before and after the administration of the hormone.
3. Kymographic recordings following repeated uterine insufflations were made before and after the administration of the hormone, in cases of amenorrhea, upon which estrin and prolan were determined.

In this communication we will limit ourselves to observations made by the first method.

The patients who were laparotomized were not chosen especially on account of their menstrual disturbances, but were those upon whom some pelvic operative procedure had been contemplated.

The hormone, a protein derivative, was administered to all of the patients in one single dose intravenously, having first tested the patient for protein sensitivity both by the intradermal and ophthalmic methods. In but one case was there a latent reaction to the hormone which manifested itself in an urticaria on the eighth day after the administration of the serum. We refrained from giving the substance to a number of patients who developed wheals after the intradermal test.

Endometrial biopsies were obtained prior to the administration of the hormone in all but two patients, these being virgin. As noted in the table, the amount of hormone used and the interval of time elapsing between the time of administration and laparotomy varied. The ovaries were examined in situ, and were either totally, or sectionally, removed for histologic examination.

DISCUSSION

As pointed out recently by Novak,³⁵ it is as difficult to differentiate the walls of an early corpus luteum from that of a maturing follicle as it is to differentiate the predecidua endometrium of a nonpregnant woman from that of a genuine early decidua. However, the criteria followed as to the age of the corpora lutea was the same as that used by Davis and Koff, namely, that of Allen, Pratt, Newell and Bland,³³ the salient features of which are: Macroscopically, as found in our investigation, the corpora were of varying sizes, measuring from 10 mm. to 30 mm., the majority of which showed recent rupture points, with a bloody fluid or gel filling the cavity. Microscopically, the stages of the corpora can be divided into three:

1. *The Stage of Formation.*—(a) The early formative stage shows a slight luteal transformation of the former granulosa cells. The latter are more follicular than luteal. There is no hemorrhage in the cavity, and there is an absence of fibroblasts

in the inner layers of the cells, which in this report is interpreted as indicating at least the first day of development after rupture. (b) The late formative stage displays many fibroblasts that have migrated through the luteal layers into the central cavity, indicating the second, or perhaps, the third day of development.

2. *Stage of Maturity*.—The theca externa and interna have reached their highest development. The theca interna contains some lipid substances and the externa consists of concentrically arranged fibers and fusiform cells and contains large blood vessels. These two connective tissue capsules are usually referred to as the wreath. The follicular cells show considerable amount of proliferation; but the luteal cells have not yet developed the yellowish characteristics of the older cells.

3. *Stage of Retrogression*.—More connective tissue than the previous stage, and this has invaded the degenerated epithelium. The cavity is smaller than in the stage of maturity, and there are present large quantities of yellowish pigment. Many of the cells contain lipid substance. The theca interna is increased in size.

Our results can be divided into four groups.

Group 1.—Those upon whom there was no ovarian response. In this group there were 6 patients who showed neither follicular stimulation nor evidence of recent ovulation.

Group 2.—Those who showed a diffuse follicular enlargement. In this group there were 5 cases.

Group 3.—Those who showed the same reaction as Group 2, as well as the presence of a current corpus luteum, but no evidence of recent ovulation. Of these there were 3 cases.

Group 4.—Those who showed follicular stimulation and evidence of recent ovulation. Of these there were 16 cases. Correlating our criteria as to the age of the corpora lutea, and the time elapsing between injection and operation, recent ovulations and follicular stimulations were diagnosed histologically as having occurred in 53 per cent of the patients.

It will be noted that most of the ovulations occurred in the first half of the cycle. Several occurred in the latter half.

In one case of amenorrhea of seven months' duration, no evidence of ovulation, either recent or current, was found, but there was diffuse follicular stimulation. In this case, there was a thickened tunica albuginea, of an almost leathery consistency. Might this not be the cause of the failure of ovulation in this case?

In two cases of cystic glandular hyperplasia, one showed a recent and current corpus luteum, while the other showed no evidence of recent ovulation. Both of the patients were admitted with a history of profuse irregular bleeding.

Endometrial biopsies taken on admission of patients bleeding, and with irregular cycles, showed various mucosal patterns, and responded differently to this gonadotropic hormone. It is interesting to note from the table that all phases of the menstrual cycle can be seen at any period in the interval. It has been our procedure in obtaining these biopsies to curette all the walls of the uterus, particularly the fundal area. Our histologic interpretations were made by our findings in the compact and spongiosa layer of the mucosa. Not infrequently, one finds a mixed pattern. In this group our conclusions were drawn from the predominant phase prevailing.

The age of the patients varied, although the younger the group, the better the response.

Why some ovaries would respond, and others would not, can be best explained, in our opinion, first, by the fact that in not a few cases were the ovaries the sequelae of chronic pelvic infection; second, that

some were approaching the menopause; third, that it can be theorized that there are variations in ovarian receptivity and refractivity in certain individuals to the gonadotropic hormone, be they exogenous or endogenous in character.

TABLE I

	CASE	AGE	MENSES		ENDOMETRIAL BIOPSY	AMOUNT OF P.M.S. ¹ INJECTION	TIME TO OPER. HOURS	OVULATION		FOLLICLES		
			INTERVAL	DAY OF CYCLE				RECENT	CURRENT	MATURE OR MATURING		ATRETIC
1	42013	42	2-3 mo.	Bleeding	Late proliferative	60 U	43	0	0	**		*
2	42210	32	Amenorrhea	7 mo.	Early proliferative	30 U	48	0	0	***Hem.		*
3	42326	18	28 days	5	Early proliferative	60 U	48	1	1	*		
4	42333	40	28 days	6 wk. prior to adm.		60 U	46	1	1			
5	42393	38	28 days	12	Late proliferative	60 U	19	2	1	**		
6	42445	30	Irreg.	10	Early proliferative	60 U	18	1	1	**		*
7	42409	23	28 days	6 wk. prior to adm.	Late secretory	60 U	18	0	1	*Hem.		*
8	42411	28	28 days	4	Early secretory	60 U	18	0	1			
9	42557	24	28 days	11	Late proliferative	60 U	21	2	1	**Hem.		
10	42563	26	Irreg.	Bleeding	Early secretory	60 U	22	0	1	**		
11	42640	31	28	9	Early secretory	60 U	22	1	1			
12	42684	17	28	10	Early proliferative	60 U	18	1	1	**		
13	42693	24	Irreg.	7	Early proliferative	60 U	24	0	1	**Hem.		
14	42730	40	Irreg.	Bleeding	Degenerated placental tissue	60 U	17	0	1	**		
15	42788	22	28	16	Early secretory	60 U	23	0	1			
16	42791	32	28	Bleeding	Hyperplasia; secretory	60 U	24	0	0	***Hem.		
17	42877	46	Irreg.	Bleeding	Early proliferative	60 U	22	2	0	**Hem.		*
18	42894	28	21	16	Cystic hyperplasia; secretory	60 U	42	1	1	**Hem.		
19	42940	33	28	16	Late proliferative	60 U	24	0	1	***Hem.		
20	42987	37	Irreg.	Bleeding	Cystic glandular hyperplasia	50 U	22	0	1	**Hem.		
21	43028	33	28	10	Early proliferative	60 U	20	1	0	***Hem.		*
22	43047	26	28	12	Late proliferative	40 U	21	0	1			
23	43066	24	28	6	Early proliferative	60 U	22	2	1	**		
24	43121	28	28	14	Late proliferative	60 U	21	1	1	***Hem.		*
25	43241	47	Menopause		Atrophic endometrium	60 U	20	0	0			
26	43295	40	28	Bleeding	Early proliferative	60 U	20	1	1	***Hem.		
27	10478	16	28	11		60 U	25	1	0			
28	18672	38	28	16	Cystic glandular hyperplasia	60 U	23	1	1	***Hem.		
29	18945	33	26	8	Early proliferative	60 U	35	2	1	**Hem.		*
30	19052	46	Irreg.	Bleeding	Early proliferative	90 U	21	0	0	Dermoid cyst		

¹Pregnant mares' serum.

*Number of follicles present.

As was shown by Hartman³⁴ in his work with this hormone on the adult monkey, and in this series on the human being, the commonest lesion consisted of a diffuse stimulation of the follicles. This was present in almost every instance where a response had occurred. It manifested itself in a granulosa cell proliferation of several layers of thickness with mitosis, cytolytic degeneration of the inner layers of the cells, perifollicular and intrafollicular hemorrhage. The question arises, in these cases, as to whether in the ovaries, if allowed to remain in situ

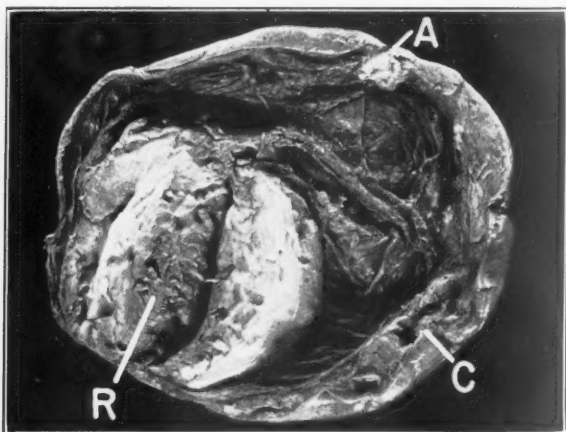


Fig. 1.—Case 42445. Recent (*R*), current (*C*), and atretic (*A*) follicles. The wall of the corpus appears completely folded. There was some hemorrhage in the folds and the cavity contained a small amount of fluid and has not redistended. The walls were pale. Eighteen hours after the administration of the hormone of pregnant mares' serum.

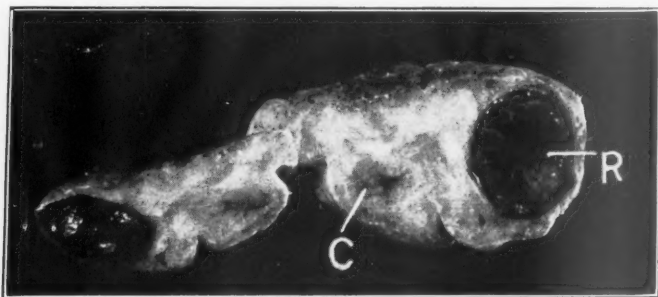


Fig. 2.—Case 43028. Recent (*R*) and current (*C*) ovulations. Note the hemorrhagic character of the recently ruptured follicle which also contains some gelatinous fluid. Twenty hours after the administration of the hormone of pregnant mares' serum.

for a longer period, would the follicles so produced progress further to ovulation, or would regression take place with the formation of atretic follicles?

In the adult monkey, where ovaries were so stimulated and allowed to remain in situ, not infrequently, the follicle would regress to that of a normal histologic structure, ovulate of its own gonadotropic stimulation, and the monkey would occasionally conceive.³⁴ The first part of

this phenomenon we have repeated in the immature *Macacus rhesus* monkey. Obviously this cannot be demonstrated in the human being. If one can use the analogy of the monkey, however, it can be stated that the manifestly deleterious action of this hormone is only temporary and that recovery is prompt and complete.



Fig. 3.—Case 42557. Gross view of a rupture point (*R*) of a recent ovulation not yet healed over. Twenty-one hours after the injection of the hormone of pregnant mares' serum.

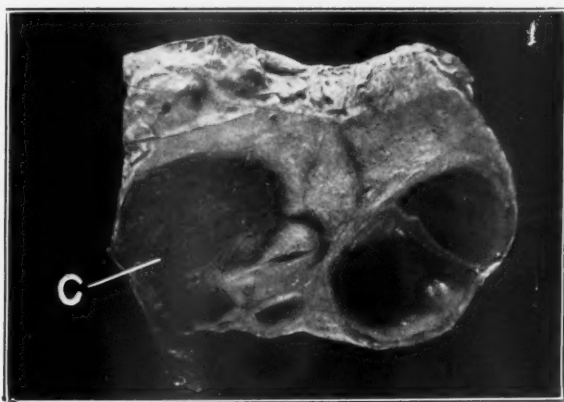


Fig. 4.—Case 18672. The current (*C*) corpus luteum is well organized and contains an old hemorrhage. Twenty-three hours after the administration of the hormone of pregnant mares' serum.

The action of this hormone, when effective, is very rapid, as shown both in the rodent and in the primate. Follicular maturation, ovulation, and corpora lutea formation can take place within twenty-four hours, and in several instances, in the human being, more than one ovulation can take place at the same time, as the result of the administration of this potent hormone.

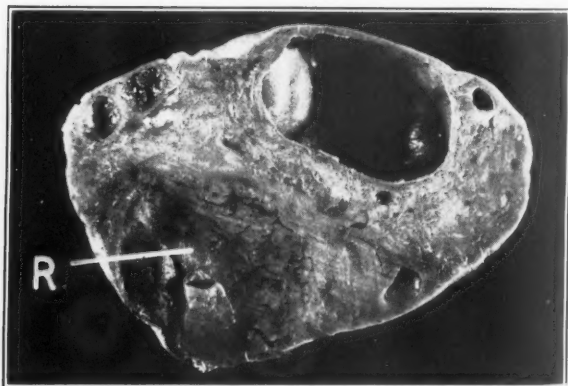


Fig. 5.—Case 18672. Note hemorrhagic cystic follicles. The lutein wall of the recent ruptured follicle (*R*) is not well developed. The cavity is distended and filled with a bloody gel.

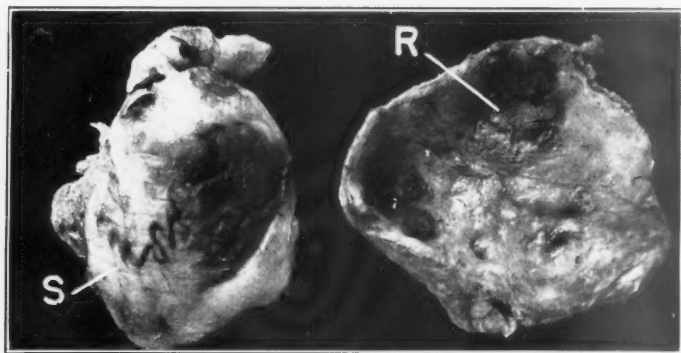


Fig. 6.—Case 42894. Gross appearance of a recently ruptured (*R*) follicle, the walls of which have collapsed, the cavity being filled with a blood-tinged fluid. Stigma (*S*) present. Several stimulated follicles also present. Forty-two hours after the administration of the hormone of pregnant mares' serum.

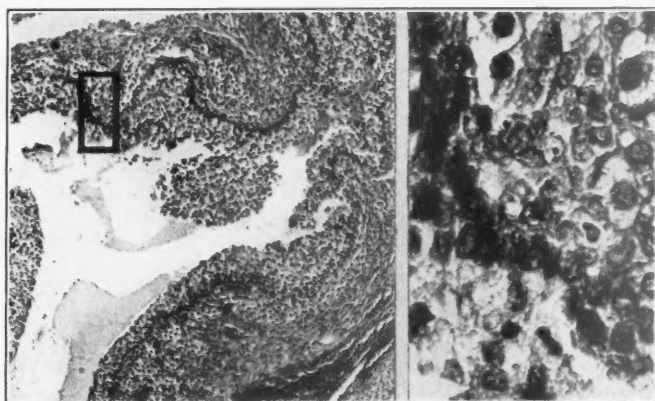


Fig. 7.—Case 42445. Eighteen hours after intravenous injection of sixty units of gonadogen. Endometrial biopsy showed early proliferative stage. Early corpus luteum of proliferation. Note arrangement of three layers. Cells of theca interna filled with light staining lipid; capillaries dilated and filled with blood. Mitosis of granulosa with streaming of coagulum. No fibroblasts in central cavity. ($\times 95$.) Mitosis and coagulum which may be interpreted as evidence of secretion. ($\times 800$.)

From a clinical standpoint, this hormone is still too new to permit an accurate evaluation as to its efficacy in gynecologic endocrine problems, particularly those due to inadequate pituitary stimulation.

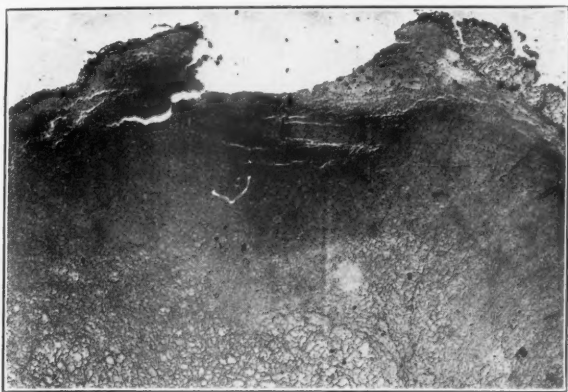


Fig. 8.—Case 42393. Nineteen hours after intravenous injection of 60 units of gonadogen. Recent rupture point filled with blood-tinged gelatinous plug. The rupture point has not yet healed by cell growth. Endometrial biopsy showed late proliferative stage. ($\times 20$.)



Fig. 9.—Case 42877. Twenty-two hours after intravenous injection of gonadogen. Early formative or proliferative stage. No hemorrhage or fibroblasts in central cavity. Slight transformation of the granulosa cells. Beginning of vascularization of the luteal layer. Endometrial biopsy showed early proliferative stage. ($\times 110$.)

From the preliminary investigations of others and one of us (S. L. S.), it seems to be of use in those cases of primary and secondary amenorrhea, which are due to failure of maturation of the follicles with corpus luteum formation, and in those cases of anovulatory bleeding due to the failure of mature follicles to ovulate. In the treatment of these con-

ditions, one should plan his injections so that he can imitate the normal phases of the cycle, for the time factor is important in the response of organs to hormones. After all, the object of treatment with a gonadotropic substance is to stimulate the ovary to normal function, and the ovarian changes should not be so rapid that the uterus cannot keep pace with the ovary.

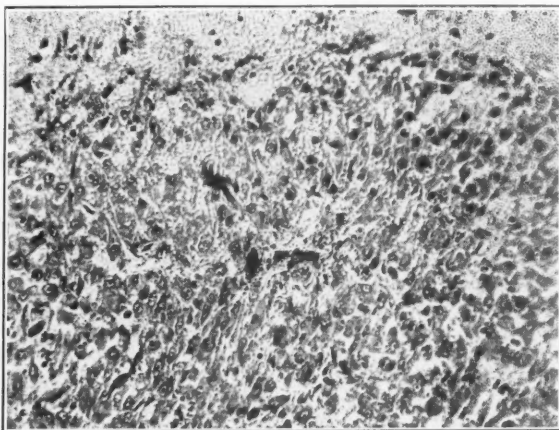


Fig. 10.—Case 18945. Thirty-five hours after injection of 60 units of gonadogen. Late formative stage. Further luteal transformation of granulosa cells; only a few fibroblasts invading the central cavity. Vascularization was not far advanced. No wreath formation. Endometrial biopsy showed early proliferative stage. ($\times 250$.)

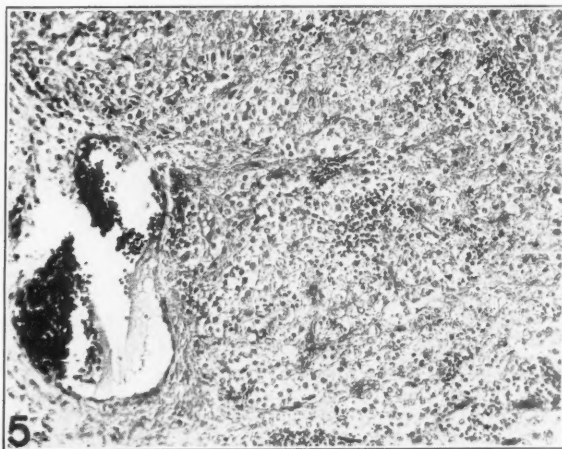


Fig. 11.—Case 42333. Forty-six hours after the injection of 60 units of gonadogen. Late formative stage. Obliteration of dividing line between granulosa cells and lutein layer. Transformation of granulosa further advanced. Hemorrhage between cell folds and in the central cavity. Migration of fibroblasts through inner layer of luteal cells. Endometrial biopsy showed early proliferative stage. ($\times 190$.)

We are slowly accumulating evidence as to the value, clinically, of this hormone. In several instances where the genital secondary characteristics have developed normally, and in the presence of primary or secondary amenorrhea, with an endometrium pattern of an early proliferative stage, and hormonal determinations showing negative estrin

and negative prolactin, menstruation was established after the administration of 10 U doses for three consecutive days, followed by intravenous injection of 30U. Where success was not obtained after a series, a second series was begun after an interval of two weeks.

Those cases of primary or secondary amenorrhea showing a persistent positive prolactin and negative estrin in their hormonal determinations, no matter what the endometrial pattern reveals, were all refractive to any type of gonadotropic stimulation. We have been successful in initiating fairly regular menstrual periods of the secretory type in several patients with anovulatory bleedings, one of whom has conceived, and delivered on April 14, 1938, of a living normal female infant of thirty-six weeks' gestation, weighing 4¾ pounds, after having been sterile for six years. Endometrial biopsies taken at many episodes of bleeding never showed an architecture of the secretory phase prior to the administration of this hormone.

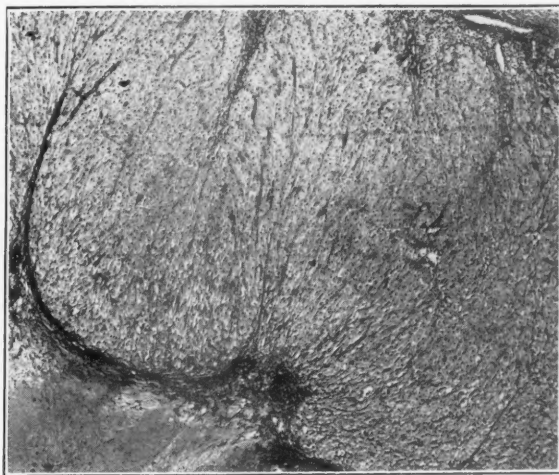


Fig. 12.—Case 42326. Forty-eight hours after injection of 60 units of gonadogen. Stage of maturity. Fairly well-developed fibroblast wreath separating luteal cells from central cavity. Lutein cells fairly well developed. ($\times 80$.)

Many of our patients received one single intravenous dose of 60 U, others, divided doses of 10 or 20 U intramuscularly daily or every other day, and still others, a combination of the intramuscular and intravenous type of injection. The latter method we believe to be the most efficacious.

It is quite possible that our failures may be due to our inability to estimate the correct dosage. One must always bear in mind, however, in the treatment of these cases, the individual receptivity and refractivity of the ovaries being so stimulated.

CONCLUSIONS

1. In many respects the gonadotropic fraction of the pregnant mares' serum closely resembles the gonadotropic activity of the extracts of the anterior pituitary.
2. Artificial ovulation has been shown to have been produced in the rabbit, the monkey, and the human being, by the use of the hormone of pregnant mares' serum.

3. Conservative and controlled clinical observations will determine the ultimate efficacy of this new hormone. Clinically, it may prove of value in those cases where gonadotropic stimulation appears desirable.

4. Being a protein derivative, prudent care should be exercised in the administration of this potent hormone.

5. We can, on the whole, substantiate the work of Davis and Koff.

We wish to express gratitude to the Upjohn Company for making this investigation possible by the liberal supply of gonadogen, the hormone of pregnant mares' serum used, and for their financial assistance. We also wish to thank Lester Bergman, M.A., for his assistance in the animal experimentation, and Henry Feintuch, M.D., Josephine Bearss, Margaret Kopicki, B.A., and A. P. Chiaramonte, B.A., for their assistance in the Laboratory at the Unity Hospital.

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706 EASTERN PARKWAY

DISCUSSION

DR. GEORGE F. CARTLAND, KALAMAZOO, MICH. (by invitation).—Dr. Siegler's observations constitute an excellent confirmation of the work of Davis and Koff in demonstrating that the mare serum hormone is capable of inducing ovulation in the human being. Since the dosage and route of administration were practically constant in this series, the variation in response may be interpreted as indicating individual differences in ovarian receptivity to the gonadotropic hormone. This has its parallel in animal experiments.

In the case of the immature rat of constant age, variations in ovarian receptivity are largely eliminated. The uniformity of ovarian response at various doses constitutes an accurate method of biologic standardization. With approximately 0.1

unit we observe a normal response as evidenced by corpora lutea of ovulation and estrus changes in the uterus. Larger doses produce tremendous enlargement of the ovaries with regressive changes in the follicles and corpora lutea atretica. Mature animals are much less regular in their response. The higher animals, such as the cat and dog, show greater variability. Hartman's work on monkeys demonstrates the difficulties of establishing a physiologic dosage, since refractory animals failed to respond to doses which produced overstimulation in others.

Similarly in the human being, the studies of Watson, Smith and Kurzrok demonstrate that with advancing age the ovary becomes refractory to gonadotropic substances. On the other hand, ovaries of high receptivity may respond to large doses with diffuse follicle development and marked ovarian enlargement. The total doses with which Kurzrok produced excessive ovarian enlargement were approximately five times as great as those reported here by Siegler.

Siegler's results, as well as those of Davis and Koff, would indicate that the total dosage for one menstrual cycle lies in the neighborhood of 60 units. Hartman's work on monkeys and Kurzrok's observations in the human being would suggest that reasonable caution should be used to avoid overdosage in susceptible individuals. Preliminary results with large doses in refractory individuals have not been encouraging.

I am glad that Siegler mentioned divided dosage. The single intravenous injection followed by laparotomy within twenty-four to forty-eight hours is a logical way to demonstrate ovulation. However, there is evidence both from animal and human experiments that, under some conditions, it may be desirable to distribute the total dosage over a sufficient time to permit the uterus to keep pace with the ovary. In applying this hormone to clinical practice the main problem is to choose a dosage and timing of injections which will induce as nearly as possible a normal physiologic response in both ovary and uterus. Siegler's data help to throw light on this important question.

Beilly has mentioned his observations on the instability of the mare serum hormone. I would like to ask Beilly if he is referring to the preparation in dry form such as gonadogen.

DR. BEILLY: I have not used the dried product but a solution of the hormone instead.

DR. CARTLAND.—During the past six years we have been studying the mare serum hormone both in solution and in the form of a dry powder. We have never been satisfied with a solution from the standpoint of stability. However, we are convinced that the dried product, as represented by the sterile vials of gonadogen used by Siegler, is reliably stable for more than a year. I believe this may be the answer to Beilly's observations on the questionable stability of the hormone in solution.

DR. ISIDOR C. RUBIN.—The matter of dosage remains still to be worked out, for the refractory elements which Siegler has referred to are factors which we do not understand. We cannot calculate for a single patient what the dosage should be. This point, by the way, holds true for practically all the hormone substances which have been elaborated in the last decade.

Of what ultimate practical use this hormone substance will be for the sterile patient cannot be stated at the present time. Davis and Koff, for example, reported 2 cases of pregnancy in a series of some 70 patients. Siegler mentioned one or two in his series. From the strictly scientific point of view we must be cautious in accepting such small percentage of pregnancies as proving the efficacy of a hormonal extract because of elements of chance. R. T. Frank has repeatedly called attention to the occurrence of such coincidental pregnancies in cases of amenorrhea which had no treatment at all, but were undergoing hormonal investigation.

It would also be desirable to have a series of patients with amenorrhea injected with this hormone. The pathology of the untreated ovaries in amenorrhea is now well known. If one could produce in such cases an appreciable number of fresh corpora lutea within 24, 48, or 72 hours, one would be convinced of the efficacy of this substance, since the ovaries associated with amenorrhea do not show active

follicle function and corpora lutea are conspicuously absent. On the other hand, if a similar series of cases were selected where the hormones of pregnant mare serum were injected a day or two after the regular menstrual cycle and the laparotomy were done within one, two, or three days, one should also be in a better position to speak of the production of fresh corpora lutea.

Another factor complicates the interpretation of these cases. The ovaries associated with pelvic inflammation, fibroids, and other conditions, frequently show corpora lutea in various stages of development and regression without these having been induced by a hormonal injection.

Whether the hormone of mares' serum will start a menstrual cycle in cases of amenorrhea has not been mentioned by Siegler. If that can be accomplished we shall have an effect comparable to that which is induced by a physical agency such as the x-rays and, in my experience also, by small doses of radium.

I was pleased to hear Siegler emphasize the importance of making a sensitization test by the intradermal and ophthalmologic application because there have been serious reactions. It is important if one is going to use the serum not to take it for granted that the patient will tolerate it but always to make certain beforehand of her reactions.

DR. JACOB S. BEILLY.—Bland and Mazer state that a great number of women seen with sterility present an anovulatory cycle. I believe that these conditions demand some form of treatment, and pregnant mares' serum seems to suggest a possible avenue of relief.

Experimental ovulation in primates has been only recently accomplished by Hisaw, who was able to produce ovulation in the monkey. He appears to have used a luteinizing as well as a follicle-stimulating hormone preparation. The synergistic action of these two combined factors, which arise from the anterior pituitary body, resulted in ovulation. Pregnant mares' serum has the biologic effect of this combination.

Our own experience with the gonadotropic hormone of the pregnant mares' serum, however, has not been as gratifying as we had anticipated, and I am of the opinion that the clinical application of this very potent preparation is not yet well known. Our assay of the preparation does not seem to hold up with the assay of the product as it originally leaves the factory. It is likely, because of its protein nature, that there is considerable deterioration between the time it is assayed at the factory and the time we are ready to use it. Having re-assayed it, we found marked differences in its potency.

DR. SIEGLER (closing).—I do feel that the hormone of pregnant mares' serum is of use in the treatment of sterile patients, particularly those on whom one diagnosis anovulatory bleeding or pituitary insufficiency as the causative factor. One can with reasonable assurance state from our histologic examination in this series that follicles are stimulated, mature, and ovulate as a result of the administration of this hormone, which is physiologically and biologically different from the hormone of pregnancy urine.

Ostensibly, there are many normal menstruating women who have episodes of anovulatory bleeding, and will, of course, be sterile during these episodes. But I hesitate to agree with Dr. Rubin that the cases of pregnancy cited were the result of just such occurrences. One of these patients, sterile for six years, received all forms of organotherapy, including x-ray treatment to the pituitary and ovaries for her anovulatory bleeding, with no change in the endometrial architecture. Not until treatment with several series of gonadogen was instituted were we able to obtain by biopsy, a secretory phase. In the sterility clinic at the Greenpoint Hospital, we were able to initiate with this hormone, the secretory phase in another patient with sterility who has had episodes of amenorrhea for three to six months, followed by anovulatory bleeding. Both of these patients have conceived.

I do not feel that this form of treatment in all cases of failure of ovulation is efficacious, for I must reiterate that there is in the human being, as well as in all other species, a specific organ response to hormones which may be refractory, and hence the patient may not respond to the administration of the hormone.

PELVIC PROGNOSIS ON THE BASIS OF RECENT X-RAY STUDIES OF THE FEMALE PELVIS*

E. C. HARTLEY, M.D., ST. PAUL, MINN.

PROBABLY our understanding of pelvic contraction has advanced as far as is possible on the basis of external pelvimetry and either manual or instrumental internal examination. The roentgenologic study of the pelvis as introduced by Thoms, by Caldwell, Moloy and D'Esopo, and others, has given us accurate methods of measurement and conceptions of form which are universally comparable. Upon the basis of this work there is growing a better understanding of the obstetric pelvis.

We have, in all of this recent work, an implication which must be kept in mind in the study of the pelvis by whatever means, namely, that we make such a study, not primarily to classify it, but to make a prognosis of labor from it: Can we deliver, with safety to mother and child, through a given pelvis? It is the special virtue of recent roentgenologic studies of the pelvis that they give us a more accurate, more easily comparable and more complete basis for making such a prognosis.

Notwithstanding the improved understanding of the obstetric pelvis, there is as yet nothing in the nature of a "mathematical formula" for the prognosis of labor. There is, however, a tendency to anticipate a prognosis of labor with more assurance than was previously possible. This anticipation is more specific than was heretofore possible, in that it directs attention to definite "trouble spots" at which the presenting part may, on the one hand, be arrested by a narrowing of the canal, or on the other, be diverted in such a manner as to interfere with the normal mechanism of labor.

In the following group of patients, the recent work of Thoms and of Caldwell and Moloy, and others,³⁻⁵ has been used to make a simple clinical classification designed to group patients according to prognosis. Within this grouping of patients, mistakes are still possible; it may, however, by forcing us at once into the ultimate purpose of pelvic study, aid us in agreeing more generally upon what is significant in pelvic form and dimension.

The classification includes three groups. A pelvis having an absolute contraction at the inlet is excluded. The three groups are as follows:

- I. Engagement being possible, labor will proceed with increasing ease.
- II. Engagement being possible, labor will proceed uniformly.
- III. Engagement being possible, labor will proceed with increasing difficulty.

*Presented before the Chicago Gynecological Society, May 19, 1939.
The roentgenograms in this group of patients were made by Mr. John S. Rose, of Dr. R. G. Allison's X-Ray Laboratories. Mr. Rose also set up the arrangement for using the Thoms grid in the lateral views.

This separation of pelves in three clinical groups should not be understood as being a dogmatic classification of pelves. It is, rather, an effort to give the clinician a point of view which loosely will include all of his obstetric patients. It undoubtedly oversimplifies the matter, but such dangers as may lie in this oversimplification may be met by qualifications which will vary somewhat according to the group into which a given patient is placed. The point of view demands the recognition of the adequate pelvis, of deviations from the adequate (handicaps), and of compensations. Fig. 1 is a schematic illustration of the three groups, in which the circle represents the pelvic inlet and the lines the birth canal below the inlet.

These diagrams (Fig. 1) represent the algebraic sum of handicaps and of compensations and are by no means intended to be diagrams of any particular pelvis.

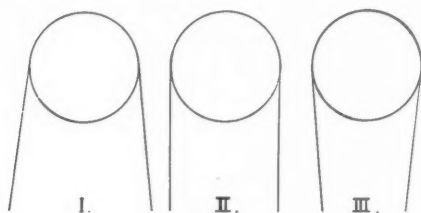


Fig. 1.

An Adequate Pelvis.—Gross deformities are not considered; in this country they are rare and may be dealt with as the occasion arises. The first criterion of an adequate pelvis is looked for in the true conjugate diameter. This is accurately read from the inlet roentgenogram, and is further checked from the lateral view. Litzmann's classic definition of a contracted pelvis gives 9.5 cm. as the true conjugate in the flat and 10 cm. for the generally contracted pelvis. Davidson² feels that a baby weighing 6.5 or 7 pounds may come through a pelvis with a C.V. of 8 cm. provided there is plenty of room in the transverse diameter. Bailey,¹ in a series of 221 generally contracted pelves, reported the spontaneous delivery of 9 whose estimated C.V. was only 8 cm. Peckman and Kuder¹⁰ classified all pelves as contracted when the diagonal conjugate measured 11.5 (C.V. of 10 cm.) or less, regardless of other measurements.

No definite minimum for the C.V. diameter can be set. Important though it is, only one of the steps in the mechanism of labor, that of engagement, is concerned with the true conjugate. Nevertheless, this *relative* importance of the C.V. is vital in any estimation of labor prognosis. For the moment, it may be considered adequate if engagement into it is possible. From this point on the classification of the patient into one of the three groups depends upon the extent to which this adequacy is added to or subtracted from by the handicaps or compensations presented by the form and dimensions of the remainder of the birth canal. No attempt will, therefore, be made to judge the adequacy of the canal below the inlet except in relation to the inlet or to other important dimensions. The tendency for the failure of a given pelvis to conform throughout to any one pelvic type (gynecoid, android, etc.) has been shown by Caldwell, Moloy and D'Esopo¹² and renders it generally impossible to base a prognosis of labor upon any one dimension. Further consideration will, therefore, be upon the basis of handicaps and of compensations.

Deviations From the Adequate Pelvis (Handicaps).—The vital, though relative, importance of the C.V. has already been mentioned. The importance of this

measurement, even at the inlet, is not absolute, but must, in most instances, be judged also in relation to inlet shape. For example, a C. V. of 11 cm. in a gynecoid pelvis which runs true to type throughout will offer no problem; even an android type with such a C. V. will often present no particular difficulty. There is this difference, however: the capacity of the fore pelvis in the android type is limited, and it will tolerate with safety less outlet or sacral handicaps than will the gynecoid.

The handicap of converging sidewalls or of a converging lateral bore is important, but, as with the C. V., this importance is relative. It is conceivable that a favorable prognosis might on occasion be given to a patient in Group III, since the inlet may have been sufficiently large to provide ample leeway for some degree of narrowing.

The importance of the biischial measurement has been recognized since Williams showed its importance as a factor in dystocia and as a criterion for the diagnosis of the funnel type of pelvis. This measurement, as it diminishes under 8 cm., becomes increasingly a handicap. Again, however, its importance is relative and must be judged, as Williams showed, in connection with the posterior sagittal diameter. It must also be judged, as shown by Caldwell, Moloy and D'Esopo,⁷ and by Schuman,⁶ in relation to the level of the sacral shelf and to the depth of the pelvis. Caldwell and Moloy found a narrow subpubic angle associated with a narrow forepelvis in 60 per cent of their cases, while wide arches showed narrow forepelves in 42 per cent. They did find, however, that narrow arches were associated with converging sidewalls in 100 per cent of the cases studied.

A high sacral shelf may become a serious handicap, all the more so since it is easily missed. Caldwell, Moloy and D'Esopo⁷ discuss the lower sacral segment at length, particularly in relation to its level as effecting extension of the fetal head at a point to coincide most advantageously with the opening beneath the pubic arch. They feel that the proper coincidence of the movement of extension from its take-off, so to speak, to its termination under the pubic arch is not solely a matter of suitable relationship between the two linear dimensions of bituberous and posterior sagittal, but of the level from which this important factor in the mechanism of labor starts.

PROCEDURE

The level and configuration of the lower sacral segment is well revealed in the lateral roentgenograms. In viewing the lateral roentgenograms, the use of a simple device is of help in quickly visualizing the level of the sacral shelf in relation to the pubic arch and the depth of the posterior pelvis. It consists of a transparent piece of stiff celluloid material ruled off in centimeter squares. The material is large enough to cover all diameters of the pelvis in the lateral view. In using it, the edge is placed so as to lie along the plane of the inlet. Such factors as the relation of the sacral tip to the ischial spines, and the posterior sagittal diameters at various levels in the pelvis may be readily visualized and measured.

Compensations.—As the term implies, compensations are favorable combinations of dimensions or form which tend to overcome handicaps. Thus, an inlet of ample dimensions may well compensate for some degree of convergence in the sidewalls or lateral bore. On the other hand, an inlet borderline in size will cause less concern if it is associated with parallel or divergent sidewalls and lateral bore; the same is true with an android type of inlet.

A wide bituberous diameter tends to compensate for a high sacral shelf; a shallow pelvis will also help greatly in this connection.

Wide lateral dimensions at the inlet tend to compensate for diminished measurements in the C. V. With such a flat type of pelvis, however, as has been pointed out by Caldwell and Moloy, there must be ample space low in the pelvis for the rotation of the head from the transverse (in which position descent has taken place) to the anteroposterior, so that extension may take place. Such space is given by a wide arch, a shallow pelvis, and a lower sacral segment giving ample posterior sagittal dimensions.

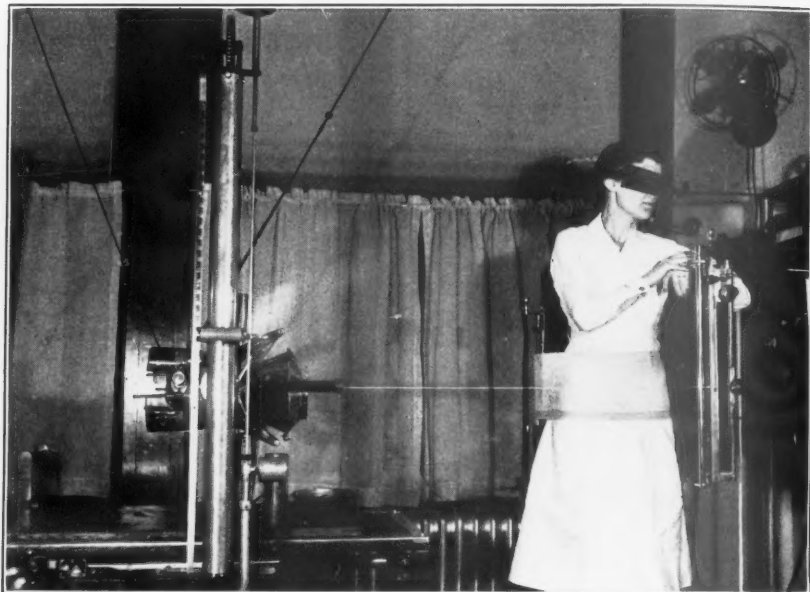


Fig. 2.—Lateral erect position at 60 inch focal film distance. 100 K.V.P., 40 M.A., time 30 to 40 sec. Erect Bucky diaphragm. The central ray is directed to a point 2 inches behind and at the level of the anterior superior spines of the ilia. A cord is stretched taut at this level, attached to the tube stand and to the center of the Bucky tray. The patient is rotated until the anterior superior spines are at an equal distance from this cord. This assures a true lateral view.

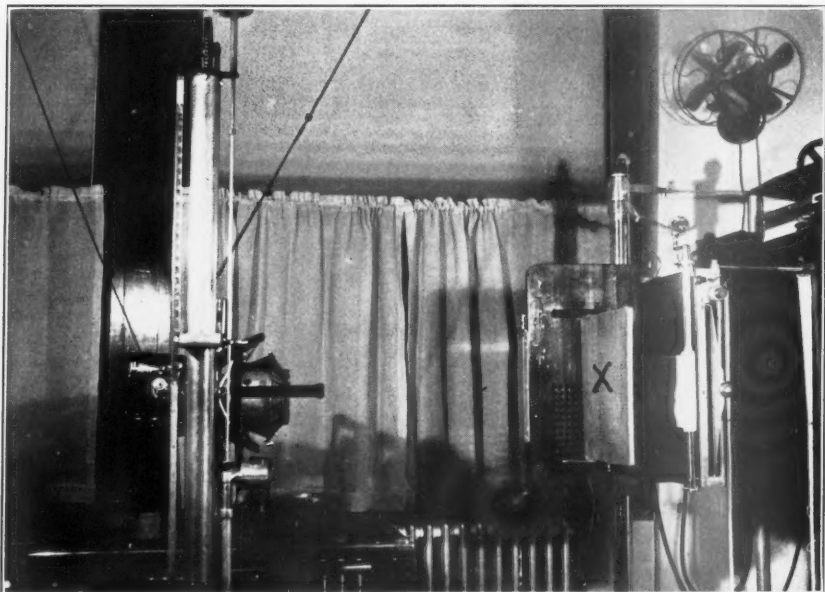


Fig. 3.—The 60 inch focal film distance minimizes distortion. The distance between the anterior superior spines is measured, after the exposure is made, and a mark is placed midway. Then the distance from this mark to the Bucky is measured and the Thoms plate or grid "X" placed at this point, as shown in Fig. 2, for the fractional second exposure, which produces the dots on the film.

The factor of the size of the fetus is obviously important but can only be discussed very briefly at this point. The size of the fetus in relation to the adequacy of the pelvis may be judged in several ways: (1) Within limits the fetus is extremely adjustable as to postural adaptation and within limits it is compressible. (2) The weight of a fetus may with experience and in an abdomen which lends itself readily to palpation be judged with considerable accuracy. (3) Various maneuvers may be carried out to determine whether or not the fetal head will enter the inlet. (4) Lateral pelvic roentgenograms will indicate the level to which the fetal head may descend into the pelvis.

The factor of forces of labor is also important. Labor pains to be effective must be strong and frequent. Their strength and effectiveness must be determined by abdominal palpation and not be interpreted from the subjective symptoms of the patient. Chemical imbalances in the blood serum of patients may occasionally seriously alter the effectiveness of the uterine contractions.

Improvement in infant mortality rates has been steady over a number of years. The decline in rate has been conspicuous in the gastrointestinal group of diseases, the contagious diseases and the respiratory group; least of all has it been observed in the neonatal group. In this group, which now include 52.2 per cent (1936),⁹ of the infants dying annually in the registration area, are the premature deaths, the birth injuries, the congenital malformations, and a number ascribed to other causes associated with the natal and prenatal period. Peckman and Kuder,¹⁰ reporting on 422 cases of "borderline" contracted pelvis delivered by the vaginal route, report a gross infant mortality of 19.23 per cent. They say, "Our experience indicates that the risk to the child is markedly increased in prolonged labor through a contracted pelvis." Thoms,¹¹ commenting on the effect upon the fetus of difficult vaginal delivery, says, "The toll of fetal deaths in such operations has received in the past too little attention." Further lowering in the present infant mortality rates must come, at least in part, through early recognition of pelvic contraction in pregnant women, and their eventual delivery planned with the type, location, and degree of this contraction in mind.

Limitations in such studies as this of pelvic form and dimensions should be kept in mind. What they represent is a part only of an anticipated plan of delivery for a specific patient. The plan necessarily has other parts, but only so far as each part becomes more and more accurate can we hope for improvement in our complete care of the obstetric patient.

The 51 cases studied in this report classified according to Thoms and to Caldwell and Moloy's method are as shown in Table I.

TABLE I

THOMS' CLASSIFICATION	THIS SERIES 51 PRI. PTS.	THOMS' SERIES ⁴		686 TOTAL
		582 CLINIC	104 NURSES	
Dolichopellic	11.7%	15.0%	37.5%	18.4%
Mesatipellic	53.0	44.8	44.2	44.7
Brachypellic I	27.3	25.0	12.5	23.1
Brachypellic II	4.0	9.3	5.7	8.7
Platypellic	4.0	5.6	—	4.7
CALDWELL-MOLOY METHOD	THIS SERIES 51 PRI. PTS.	PETTIT, ET AL. 100 PRIM.	CALDWELL, MOLOY AND SWENDSON ¹³	
Gynecoid	55.0%	51.0%	50.6%	
Android	27.5	21.0	22.4	
Anthropoid	11.7	18.0	22.7	
Platypelloid	5.8	5.0	4.4	
Asymmetrical	—	5.0	1.8	

CONCLUSIONS

In the absence of a "formula" upon which to base a prognosis of labor, the approach above described has been found useful as a tentative means of using the findings of recent x-ray studies clinically. Beginning with the form and dimensions of the inlet as a point of departure, or base, the progress of labor from that point on is pictured as falling into one of three possible groups. The criteria which place a given pelvis into one particular group are found in varying combinations of form and dimension in the sidewalls and lateral bore, the lower sacral segment, pelvic depth, and the bituberous diameter at the outlet. These criteria are variables within any classification of pelvis and, hence, for each individual pelvis, must be checked against each other as a series of handicaps or compensations whose algebraic sum gives us our prognosis.

SUMMARY

1. A method of classifying pelvis according to expected prognosis of labor is presented. The classification is based upon recent advances in pelvic roentgenography of Thoms, of Caldwell and Moloy, and others.
2. The use of Thoms' grid in lateral views of the pelvis is discussed.
3. A simple device to aid in visualizing certain relationships in the lateral roentgenograms is described.
4. A series of cases is presented with an analysis of several on the suggested prognostic basis.

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DISCUSSION

DR. WILLIAM B. SERBIN.—The classical contributions to our knowledge of the obstetric pelvis, more especially with reference to the classifications of Michaelis, Litzmann, Schauta, and Breus and Kolisko, are gradually being supplanted by the recent and more accurate observations of Caldwell and Moloy and Thoms. Whereas, the observations of these obstetricians could only be limited to a study of dry pelvis and crude measurements in the living, the modern investigator has had the advantage of refined x-ray technique. Even x-ray has had to undergo various stages of experimentation from the original simple plate to the present opportunity of almost perfect measurements by the screen grid technique of Thoms or the stereoroentgenoscopic method of Caldwell and Moloy.

I agree, therefore, with the essayist's opening statement that "our understanding of pelvic contraction has advanced as far as is possible on the basis of external pelvimetry and either manual or instrumental internal examination."

Dr. Hartley now proposes to make a prognosis by means of pelvic roentgenometry. His criteria are measurement of the conjugata vera, depth of pelvis, character of lateral pelvic walls and pubic arch, and contour of the sacrum, etc.

Exclusive of extreme contraction, three types are recognized, based on engagement: (1) Labor proceeding with increasing ease; (2) labor proceeding with uniformity; (3) labor proceeding with increasing difficulty. This classification is desirable because it attempts a prognosis upon our borderline cases. While his series is admittedly small, his analysis has been meticulously worked out.

Many of you would like to know the feasibility of routine x-ray during pregnancy or labor. True, special apparatus and special technique are necessary; the method requires two views, and finally it is expensive. When we bear in mind that 85 per cent or more patients have normal or nearly normal deliveries, it is obvious that x-ray pelvimetry is not necessary in this group. The remaining 15 per cent, and these give some evidence beforehand, viz., contraction of inlet, convergent pelvic walls, decreased lateral bore, narrow arch, "shelving of sacrum," some such method is highly desirable. X-ray pelvimetry does not and should never supplant clinical judgment.

Dr. Hartley should collect a larger series, and give the Caldwell and Moloy and Thoms' classifications and their revisions of the mechanism of labor a more severe test.

THE TREATMENT OF AFTERPAINS AND PAINFUL ENGORGEMENT IN THE PUERPERIUM WITH TESTOSTERONE PROPIONATE

A PRELIMINARY REPORT

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AMONG the most common and distressing complaints of the puerperium are afterpains in multiparas, and painful engorgement of the breasts, usually in primiparas. This report presents our experiences with the use of the so-called male sex hormone, testosterone propionate, in the relief of these conditions.

Briefly stated the therapeutic rationale for the use of testosterone propionate is as follows: All the sexual hormones are definitely bisexual in their action, though to a varying degree.¹ Embryologically,² as well as biologically,³ the female gonad exhibits strong bi-sexual potentialities. Normal human females excrete from one-sixth to as much androgenic substances in their urine as do normal men.^{4, 5} Testosterone is not only strongly androgenic, but it is also a very potent gynecogen, especially as regards its stimulative action on the female genital tract.¹ Its action is dual, however, in that it resembles estrogens in many respects,⁶ yet on the other hand it may simulate the action of progesterone.⁷⁻⁹

Testosterone will inhibit rhythmic, intermittent contractility of the uterus as well as desensitize it to the action of pituitrin.^{8, 9} The exact action of testosterone on the human breast is not yet known.¹⁰ Therefore its use in mastalgias is purely empirical.

Clinically, we have found that testosterone propionate will relieve dysmenorrhea.¹¹ In addition, it was noted that premenstrual breast tension was also relieved.

Proceeding on this experimental and clinical evidence, we began to treat afterpains and painful engorgement of the breast in the puerperium with testosterone propionate.

I. AFTERPAINS

The etiology of this condition is not known. However, most observers seem to agree that relatively excessive contractions seem to be the immediate cause of the pain,¹² probably resulting from a transient local ischemia.¹³

First it was decided to employ testosterone propionate (t.p.) to prevent afterpains. For this purpose 100 multiparas (almost all private patients) were chosen, 75 serving as controls. Both groups were similar in average age, parity, and duration of labor. Analgesia and anesthesia were also similar. Each group received a course of 6 doses of ergonovine, gr. 1/320, during the first two days of the puerperium. The test group received 10 mg. of testosterone propionate by deep subcutaneous injection in the deltoid region, fifteen minutes to two hours after the third stage of labor.

In the control group of 75, 24 per cent (18) had little or no discomfort, 56 per cent (42) received marked to moderate relief with two to four doses of codeine (gr. i) or ten doses of acetylsalicylic acid (gr. x. q. 4 h.), while 20 per cent (15) required several doses of codeine over a period of thirty-six to seventy-two hours.

In the test group, 88 per cent (22) had no pain at all or an occasional vague pain, usually after an ergonovine tablet, which required no analgesia. Of the three who failed to get relief, one received complete relief with an additional 5 mg. of testosterone propionate ten hours later, one received marked relief with an additional injection of 5 mg. of testosterone propionate twelve hours later, and the third one failed to get relief with 30 mg. of testosterone propionate.

Forty-nine patients with severe afterpains, many of whom had failed to respond to ordinary analgesia, were treated in the following way: Five milligrams of testosterone were given intramuscularly and one hour later 5 mg. more subcutaneously in order to sustain the initial reaction over a longer period of time. In some cases 10 mg., divided between the two routes, were given at one time. Relief was usually apparent in from twenty minutes to an hour. Therapy was successful in rendering adequate relief in 82 per cent (41) of the patients treated. Of the remaining 8, 2 secured complete relief with an additional 5 mg. Six (13 per cent) received little or no relief, even with 20 mg. in two cases, and 15 mg. in 3 cases.

No effect on lochia or on lactation was noted. It was the general impression that involution of the uterus was definitely hastened, but unfortunately this observation was noted too late for statistical study.

No correlation could be made between the occurrence of afterpains and a previous history of dysmenorrhea.

II. PAINFUL ENGORGEMENT

Engorgement of the breasts usually begins thirty-six to seventy-two hours after delivery and may become very painful six to twenty-four hours later, lasting from six hours to three days. Engorgement is much more likely to be painful in primiparas, in those who do not nurse, in those whose babies nurse poorly, or in those who wean their babies for one reason or another. Pain is much more likely to occur where the breasts are small. The pain may be centered about the nipple or be situated at the upper, outer quadrant of the breast.

Fifty cases of severe painful engorgement of the breasts were treated with testosterone propionate. Many of these had failed to receive relief with an adequate tight uplift binder, ice caps, and analgesics.

Treatment consisted in stopping previous medication, and giving 5 mg. of testosterone intramuscularly and another 5 mg. subcutaneously an hour later. Relief was usually apparent in one-half to one hour and was practically complete in three to six hours. Occasionally a mild transient galactorrhoea was noted. The breasts generally became completely soft in three days, if the baby did not continue to nurse. In mothers who continued to nurse their babies, no inhibition of lactation was noted. This was checked by weighings. No ill effects of any sort were evident in the babies.

Of the 50 patients treated (44 primiparas and 6 multiparas), 92 per cent (46) obtained practically complete relief. Of the remaining 4, 1 obtained marked relief with an additional 5 mg., 1 obtained questionable relief with 10 mg. more, and 2 failed to receive any relief.

DISCUSSION

In its effect on afterpains, testosterone behaves similarly to "progestin"¹⁴ in the alleviation of the pain. Motility does not seem to have been completely inhibited, however, because occasionally contractions could be felt under the hand after the pain had subsided.

The accelerated involution of the uterus is perhaps explainable on the effect of testosterone upon the myometrium. By reduction of motility, the volume flow of blood to the uterus is reduced.¹⁵ By the direct stimulative action of testosterone on the myometrial elements,¹⁶ the volume flow of blood in the myometrium is reduced. Since growth of the uterus is dependent on its vascular status,¹⁵ it seems clear that the net result of the relative anemia caused by the action of testosterone will be to hasten involution.

The effect of testosterone on painful engorgement of the breast cannot be explained on the basis of our present knowledge, since the effect of testosterone on the human breast is not adequately known.¹⁰ That the action is not through inhibition of lactation is attested by the fact that lactation was not inhibited in any of the patients who continued to nurse their babies.

SUMMARY AND CONCLUSION

Testosterone propionate in a dose of 10 mg. subcutaneously, given within two hours post partum, prevented afterpains in 88 per cent of the cases.

In a series of 49 patients with severe afterpains, adequate relief was obtained in 82 per cent with a total of 10 mg. of testosterone divided between the intramuscular and subcutaneous routes.

In 50 patients with severe painful engorgement, it was found that 10 mg. of testosterone propionate (5 mg. intramuscularly and 5 mg. subcutaneously an hour later) gave practically complete relief in 92 per cent of the cases. No inhibition of lactation was noted in those mothers who continued to nurse their babies.

I wish to thank Dr. M. W. Aaronson, Director of Obstetrics, for his keen interest and his kind permission to conduct this study. Also I wish to acknowledge with grateful appreciation the invaluable assistance afforded by S. H. Kintberger, R.N.

The testosterone propionate (Perandren) used in this work was kindly supplied by Dr. Ernst Oppenheimer of Ciba Pharmaceutical Products, Inc.

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THE DETERMINATION OF RUPTURE OF THE MEMBRANES

A COMPARATIVE STUDY

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RECENTLY there has been considerable interest in the establishment of accurate tests for the determination or confirmation of rupture of the amniotic sac. The tests have been based on the fact that normally the hydrogen ion concentration (pH) of the vaginal secretion ranges around 4.5 to 5.5 and the pH of the amniotic fluid is 7.0 to 7.5. On the assumption that the pH of the vaginal secretion will change when it is contaminated with the escaping amniotic fluid following rupture of the membranes, the determination of the hydrogen ion concentration of the vaginal secretion would seem to be an index to the continuity of the amniotic sac.

Baptisti¹ using nitrazine paper* in a series of 50 cases concluded that the test might be used as a test for determination of ruptured membranes. King² using applicators dipped into a 0.2 per cent alcoholic solution of bromthymol blue found this test accurate in 99 per cent of cases with intact membranes and 95 per cent of cases with ruptured membranes.

To determine the efficacy of these tests it was planned to run a series of cases. This would at the same time enable us to compare the methods.

TECHNIQUE

Fifty patients, consecutively admitted to the ward delivery room of The Bronx Hospital, were used in this series. The pH of the vaginal secretion was determined by both methods, viz.: (a) a sterile cotton-tipped applicator was inserted deeply into the vagina and after withdrawal, the cotton tip was touched to a strip of nitrazine paper and the paper then compared with a pH color chart; (b) a sterile applicator saturated with bromthymol blue was inserted deeply into the vagina and after withdrawal read directly, ruptured membranes being denoted by a green color at the tip of the applicator.

TABLE I

ADMISSION HISTORY	TOTALS	BROMTHYMOL BLUE TEST		NITRAZINE TEST		OPERATOR'S REPORT POST DELIVERY	
		INTACT	RUPTURED	INTACT	RUPTURED	INTACT	RUPTURED
Intact	35	26	9	34	1	35	0
Ruptured	8	4	4	2	6	0	8
Unknown	7	6	1	4	3	3	4

*Manufactured by E. R. Squibb & Sons Co., N. Y., paper impregnated with sodium dinitro phenylozonaphthol disulphonate and set at a pH of 6.0 with a range of from 4.5 to 7.5.

RESULTS

Table I shows the results obtained in the 50 cases studied. In 35 cases admitted with a history of intact membranes, the bromthymol blue test was accurate in 26, or 74 per cent, while the nitrazine test was correct in 34, or 97 per cent. In 8 patients admitted with a history of ruptured membranes the bromthymol blue test was correct in only 4 cases, or 50 per cent, while the nitrazine test was correct in 75 per cent. Of the 7 patients admitted with an unknown history, again the bromthymol blue test was correct in only 50 per cent of the cases, while the nitrazine test was accurate in 75 per cent.

SUMMARY

1. The admixture of alkaline amniotic fluid to the normally acid vaginal secretions changes the reaction in the vagina.
2. The resultant pH may be indicated by bromthymol blue or nitrazine test papers.
3. The use of nitrazine test papers, in our hands, gave a much more accurate result.
4. The test lends itself ideally in those patients who present themselves with a history of possible rupture of the membranes, in whom the usual clinical examination is not adequate to confirm the history.

I wish to express my thanks to Dr. Samuel J. Stein for his assistance in reading the determinations; and to Dr. Meyer Rosensohn, attending obstetrician, for his kindly interest and helpful suggestions in the preparation of this report.

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ERRORS IN DIAGNOSIS OF HYDROCEPHALUS IN THE BREECH PRESENTATION

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IT IS well known that the fetal head, when in the fundus of the uterus, often feels larger to the examining fingers than normal. It is less generally realized that flat anteroposterior roentgenograms of such infants may also give an exaggerated conception of fetal head size and may lead, particularly when correlated with the findings on palpation, to an erroneous diagnosis of hydrocephalus. During the past year, two cases have come to our attention in which mistaken diagnoses of hydrocephalus were based on anteroposterior roentgenograms, and in one of these a normal fetus narrowly escaped a destructive operation on the aftercoming head. With the increasing employment of x-ray in obstetric diagnosis, it would seem desirable to note this particular pitfall

and to establish, if possible, definite criteria for the interpretation of x-ray films in which a large fetal head is shown in the fundus uteri. Brief histories of the two cases follow:

CASE 1.—T. B. G. (Baltimore City Hospitals.) The patient was a 19-year-old, colored primigravida, with a normal pelvis and a negative blood Wassermann, whose last menstrual period began on June 7, 1937, making her estimated date of confinement about March 14, 1938. She was registered in the Baltimore City Health Clinic, where she was followed through an uneventful prenatal course. She fell into labor spontaneously at 3 P.M., on March 22, 1938, and was admitted to the hospital in mild labor on the following morning. At that time, an anteroposterior roentgenogram, taken at a distance of thirty inches, was obtained on the suspicion of a twin pregnancy, but revealed a single fetus in L.S.T. position. Since the head appeared to be very large, a diagnosis of hydrocephalus was made and preparations carried out for craniotomy on the aftercoming head. A photograph of the x-ray plate is shown in Fig. 1. After twenty-nine hours of labor, rectal examination revealed the cervix to be fully dilated and the fetus in frank breech deeply engaged. Delivery of the trunk, extremities, and shoulders was effected in the usual manner; surprisingly enough, the head followed at once, being delivered easily by the Mauriceau maneuver. The child was a normal male, in good condition, and weighed six pounds (2,725 gm.). The fetal measurements obtained at birth are recorded in Table I, together with those obtained from the x-ray plate.

TABLE I. FETAL MEASUREMENTS OBTAINED AT BIRTH TABULATED AGAINST THOSE OBTAINED FROM THE ANTEROPOSTERIOR ROENTGENOGRAM

DIAMETER	X-RAY (CM.)	BIRTH (CM.)
Occipitomenal	18.4	13.5
Occipitofrontal	16.6	11.5
Suboccipitobregmatic	12.2	8.5
Biparietal	—	9.0
Bitemporal	—	8.0
Total length	—	40.0
Weight	—	2,725 gm.

CASE 2.—R. S. C. (Johns Hopkins Hospital x-ray files.) The patient was a 28-year-old, white primigravida, with a funnel pelvis, whose last menstrual period began on Jan. 29, 1936, making her estimated date of confinement about Nov. 5, 1936. The pregnancy progressed uneventfully. Since the fetal position during the last lunar month was consistently found to be a breech, and since the fetal head appeared to be rather large on abdominal palpation, a single anteroposterior roentgenogram was obtained at a physician's office on Oct. 27, 1936. The exact tube-film distance is not known, but was presumably short. On the basis of the exaggerated fetal head shadow, a diagnosis of hydrocephalus was made; the measurements from this fetal head shadow are included in Table II.

On October 29 cephalometry, after the stereoscopic method of Hodges,¹ was performed on this patient and one of the lateral plates from this series is shown in

TABLE II. FETAL MEASUREMENTS IN CENTIMETERS, OBTAINED SOON AFTER BIRTH, TABULATED WITH THOSE OBTAINED FROM THE ORIGINAL ANTEROPOSTERIOR ROENTGENOGRAM AND FROM ONE OF THE LATERAL STEREOSCOPIC FILMS. THE UNCORRECTED CALCULATIONS FROM THE LATTER ARE INCLUDED

	FLAT PLATE	BIRTH	LATERAL STEREOSCOPIC FILM	CALCULATIONS FROM LATTER
Occipitomenal	18.3	—	14.3	11.7
Occipitofrontal	17.5	11.5	13.7	11.0
Suboccipitobregmatic	13.0	—	11.1	9.0
Biparietal	—	10.0	—	—
Weight	—	3,175 gm.	—	2,800 gm.

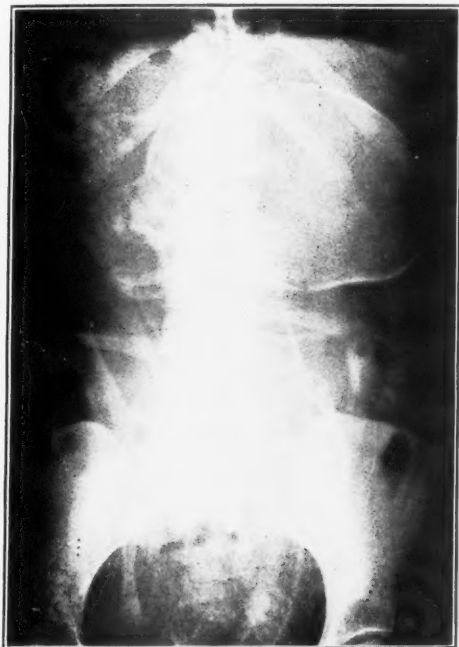


Fig. 1.—Anteroposterior roentgenogram from Case 1, from which the diagnosis of hydrocephalus was erroneously made. Note the absence of characteristics of hydrocephalus and the tendency toward occipital flattening. Tube-film distance of 30 inches employed.



Fig. 2.—Lateral roentgenogram from Case 2. This is one of the stereoscopic films from which calculations of fetal size were made by the Hodges method. Note the normal appearance of fetal head size and shape. Tube-film distance of 36 inches employed.

Fig. 2; this is reproduced, rather than an anteroposterior one, since in the latter an oblique view of the fetal head was obtained. From the stereoscopic films a diagnosis of a normally formed fetus was made, and the resulting uncorrected figures for fetal head size are recorded in Table II. Because of the funnel pelvis and breech position, an elective cesarean section was performed on October 31, and a normal male child, weighing 7 pounds (3,175 gm.), was delivered in good condition. Measurements obtained soon after birth appear in Table II.

DISCUSSION

A comparison of some of the above figures will reveal that simple divergence of x-rays can account for an exaggeration of fetal head shadow amounting to more than 50 per cent when the fetal head lies in the fundus and is viewed from the anteroposterior position. This large amount of distortion is due to the fact that when the fetus presents by the breech, its head lies at a greater distance from the film than when the fetus lies in an occipital position; in cases of the latter position the distortion rarely amounts to as much as 25 per cent. The added increase in distortion of the fetal head when it lies in the fundus, may be avoided by obtaining the roentgenogram with the patient in the lateral position, for in this position the fetal head will gravitate to a lower level and will approach the film more closely than it possibly could with the patient lying on her back.

Furthermore, if one will view in a stereoscope the films of a fetal head that is suspected of being hydrocephalic, the size will be much less exaggerated than when viewed on a simple flat plate, and this is particularly true when some type of precision stereoscope is employed. Today, however, the use of any of the accepted methods of cephalometry (such as: Thoms,² Walton,³ Ball,⁴ Hodges,¹ Clifford,⁵ or Johnson⁶), should avoid the possibility of erroneous diagnoses of intrauterine hydrocephalus made solely on the basis of exaggerated fetal head size.

Roentgenologists recognize several distinguishing characteristics of intrauterine hydrocephalus, and these should always be sought for when the fetal head appears, in any roentgenogram, to be unusually large. Among these are: the relatively small facial features, gaping sutures and fontanels, disproportionately small body and the globular shape of the fetal head. A normally developed fetal head rarely shows any tendency toward a globular shape when lying in the fundus. On the contrary, there is usually the suggestion of flattening of the occiput and this is best seen in Fig. 1 and was noted after delivery in the fetuses of both cases here reported.

The x-ray diagnosis of intrauterine hydrocephalus with the fetus in breech position should never rest on the apparent size of the head in a flat anteroposterior plate, but should be based only upon one of the other characteristics enumerated above.

CONCLUSIONS

1. The diagnosis of intrauterine hydrocephalus from flat anteroposterior roentgenograms when the fetus presents by the breech is hazardous.

2. Flat lateral roentgenograms or stereoscopic films will aid in avoiding an erroneous interpretation.

3. Cephalometry by any recognized position or stereoscopic method will reveal the true size of the fetal head.

4. An enormous fetal head shadow must include at least one of the characteristic features of hydrocephalus before such a diagnosis can be safely made.

5. To the usually accepted roentgenographic characteristics of intrauterine hydrocephalus, we should like to add: (a) the absence of occipital flattening in cases of breech position; and (b) the marked decrease in density of the vault of the skull, as observed by haziness of the fetal head shadow in this region, when compared with that of the base of the skull.

We wish to thank Dr. Louis H. Douglass, Chief of Division of Obstetrics at Baltimore City Hospitals, for the privilege of reporting Case 1; and Dr. Alan F. Guttmacher, Associate Professor of Obstetrics, Johns Hopkins University and Hospital, for allowing us to include Case 2.

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IRRADIATION OF CANCER OF THE CERVIX

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THE end results of 158 cases of carcinoma of the uterine cervix treated with roentgen rays and radium in the Radiation Therapy Service at Bellevue Hospital from 1925 to 1930 were reported by Kaplan¹ in 1932. This presentation is a continuation of that series with a report of 677 patients observed during the period 1925 to 1937. In all but 3 of these the diagnosis was confirmed by sections examined by the pathologist to the hospital.

THE TYPE OF MATERIAL AT BELLEVUE HOSPITAL

In 232 patients the disease was so far advanced at the time of their admission that they had to be transferred to the City Cancer Institute for custodial care. The remaining 445 patients were treated in Bellevue Hospital, and of these 263 had either unilateral or bilateral parametrial involvement and 136 received only partial treatment. The type and immediate disposition of this group of cases is shown in Table I.

In this series of Bellevue Hospital cases we include 396 patients who had had no treatment for their malignancy prior to admission to the service, 16 patients who had had a previous hysterectomy and 33 who had x-ray or x-ray with radium therapy elsewhere and were then referred to our service for radiation therapy, either as a prophylactic procedure or for treatment of an evident recurrence.

TABLE I

Patients transferred to City Cancer Institute	232
Patients who had hysterectomy before admission	16
Patients treated by radiation before admission	33
Patients in whom treatment was begun but not completed at Bellevue	136
Patients who had complete therapy at Bellevue	260
Total	677

EXTENT OF DISEASE

This study has been undertaken without grouping the patients, because it was felt at the time that the clinical classification of cancer of the cervix depended so much on individual interpretation as to be of little value. The method for classifying the types of cancer of the cervix now being attempted at Bellevue Hospital is based on the anatomic classification adopted by the Cancer Committee of the League of Nations.

We rarely see a patient with a cervical cancer before the ulceration and infiltration have extended into the involved deeper cervical tissues. Until the past four or five years, in fact, no cases could be placed in Group I, while a great number were in Group IV.

SYMPTOMS

When admitted to the service the most frequent symptoms of which the patients complained were metrorrhagia, pain in the lower quadrants of the abdomen, irregular menses with intermittent spotting, and irregular prolonged periods. Clinic patients usually do not keep careful records of their menstrual cycle, but increased frequency of the menstrual period is the most common change that influences a woman to seek a doctor's advice. The severity of the hemorrhage does not, in all instances, indicate the extent of the disease, nor does a long history of symptoms necessarily mean that the case is hopeless.

Pain is usually present in patients with secondary inflammatory adnexal or broad ligament involvement; in no instance was pain present when the growth was localized in the cervix. Invasion of the rectum and of the bladder produces characteristic symptoms, while lateral invasion may result in pressure on the nerve trunks with pain radiating to the lower extremities. In other instances pressure over the lymphatics and veins causes swelling of one or both extremities.

ROUTINE THERAPY

In the treatment of carcinoma of the cervix, neither x-rays nor radium should be employed alone. Patients, we observed, who had had an incomplete course of therapy either in our clinic or in some other hospital, did not have a favorable outcome. The roentgen ray treatment in the Bellevue clinic is usually started as soon as diagnosis is established. This therapy is followed by radium and later by a second course of x-ray.

Diagnosis.—In addition to the routine palpation and inspection of the cervix, digital rectal examination is always done to determine the condition of the parametria and lymph nodes located at the bony pelvis. At times proctoscopic examination of the lower sigmoid and rectum is performed to discover possible extension of the disease to these parts. Routine cystoscopic examination is highly advisable, and for several months we have established this procedure as a routine measure. In quite a few patients occlusion of a ureter was found as the result of invasion of the ureteral walls or from pressure of involved adjacent lymph nodes.

1. *Preradium X-ray.*—As soon as diagnosis is established, x-ray therapy is commenced. Until 1929 the technique of irradiation as employed by us was one skin erythema dose to each of four areas of the lower pelvis, anterior right and left, and posterior right and left, one-quarter dose administered over two areas daily. Since 1929, higher doses were delivered and a larger number of areas were treated; namely, two anterior and two posterior lower pelvic areas, two lateral to affect parametrial involvement and in cases with bulky cervical masses, vulva and anal areas were added. The dose administered was 1,200 to 2,400 r. to each portal. To

the vulva and anal areas, however, only 900 to 1,000 r. were given, as severe epidermitis develops after this amount of irradiation.

2. *Radium*.—Vaginal application of radium follows the completion of the preliminary course of roentgenotherapy. Radium, in a rubber sound, is inserted into the uterine canal and a colpostat with two or three corks is placed against the cervix, and held in place with several pieces of iodoform gauze packing. The radium is filtered through 1.5 mm. platinum in the sound and 2.5 mm. platinum in the colpostat. The radium applicators remain in situ for 96 to 120 hours. After the radium is removed, the patient is discharged in one or two days if no untoward effect has occurred. She returns for observation every two weeks thereafter.

Upon completion of this series, radium was applied using a sound in the uterine canal and a colpostat with two or three corks against the cervix, held in place with iodoform gauze packing, and a total dose of 5,000 to 7,000 mc. hr. administered.

3. *Postadium X-ray*.—Since 1929, an additional course of x-ray, following the radium, has been given. With the use of the saturation method, as suggested by Pfahler, higher doses can be delivered without damage to the skin. This method is employed by us in order to deliver the maximum amount of irradiation to the tumor bearing area. In many instances of very advanced cases in which the treatment was given as a palliative measure, healing of ulceration with cessation of bleeding and discharge has followed with improvement in the general health of the patient.

The postadium course of x-ray therapy is given at the end of two months, or as soon as the radium membrane on the vaginal mucosa has disappeared. It is directed as a rule through four portals, but in advanced cases with residual parametrial involvement, two lateral portals are added. The dose administered was 1,200, 1,800, or 2,400 r/u to each portal. The factors used were 200 kilovolts, 8 to 20 milliamperes, 40 to 50 cm. target distance, and filters of 0.5 mm. copper plus 1.0 mm. aluminum, administered at the rate of 16 to 50 r/u per minute.

Complications.—In some patients x-ray treatment had to be terminated prematurely when the skin reaction reached a third degree epidermitis, or actual blistering of the skin. Daily applications of aquaphor ointment were very helpful. Changes in the mucosa of the vaginal wall were rarely observed, even when the vulval and anal areas were treated. This was due to the comparatively small dose applied to these regions, and because the amount of irradiation reaching the vaginal wall from the pelvic areas was too small to cause changes in the mucous membrane.

While the protracted irradiation was being administered, vaginal and bowel hygiene were carefully observed, and the general condition of the patient was improved by means of proper diet and transfusion when necessary.

Bladder irritability, except for a transient frequency of urination, was unusual. Intestinal disturbances were more constant and were manifested by diarrhea and cramps lasting several days, in a few cases only did it last longer and cause prostration and loss of weight. These symptoms are usually combated by hospitalization and such supportive measures as transfusions and infusions of saline, and glucose were indicated only after the following routine procedures failed to control the symptoms.

1. Citrous fruit juices are given routinely after each treatment to control acidosis.
2. Bicarbonate of soda will sometimes relieve the symptoms.
3. Calcium gluconate before meals in 15 gr. doses.
4. Liver extract per os or intramuscularly.
5. Vitamin B per os or intramuscularly.
6. Nembutal or other sedatives.
7. Adrenalin 1:1000, 3 or 4 min. per os 5 minutes before starting treatment.
8. Friedman's mask.
9. Ice cold ginger ale.
10. Rectal taps may be necessary and one may even have to resort to hypodermoclysis in certain instances.

Pelvic infection was a more serious but rarer complication. The most important aspect of this problem is the prevention of infection. Especially to be feared is latent gonorrheal involvement of the adnexa which may be lighted up by radiation.

In all cases immediate removal of the radium is indicated if the temperature rises to 103° F. or more, the treatment being completed only after the infection subsides. Later pyometra is avoided by promoting adequate drainage from the uterine canal by frequent insertion of a sound in the canal to prevent its occlusion by adhesions. If the radium is re-applied in such cases a modified procedure is used. Dilatation and reposition of the radium in the uterocervical canal is avoided for fear of another flare-up of the pelvis infection. Radium needles are sometimes inserted in such a way as to surround the uterine cervix, and the colpostat is replaced as originally. The postradium course of x-ray therapy in these cases is more intensive, in order to affect residual malignancy.

SPECIAL TYPES OF TREATMENT FOR UNUSUAL SITES OF GROWTH

In a few patients where the recurrence was located on the lateral vaginal wall a mold or a special applicator with radium tubes was constructed and placed against the involved area, thus providing direct contact irradiation to the lesion. The other parts of the vagina are protected by a lead shield and gauze packing.

In patients where the rectovaginal wall was involved a specially constructed proctostat bearing a number of radium tubes was placed in the rectum and an applicator placed in the vagina, thus providing crossfire irradiation to the involved area.

In malignant infiltration of the anterior vaginal wall a specially constructed applicator was inserted into the vagina, in contact with the lesion.

In some patients with a bulky tumor mass formation radium needles were inserted parallel to the urethra. A retention catheter was always used in these patients.

In one case a histologically proved metastasis to the tibia occurred three and one-half years after irradiation.¹¹

END RESULTS

In evaluating the results from treatment of cancer of the cervix, it has been generally accepted that a patient who is alive and free from clinical evidence of the disease five years or more after treatment is a successful case. For this reason the results in only 276 malignant cases seen and treated during the period from 1925 to 1933 are discussed.

TABLE II. END RESULTS

	TOTAL	NO. DEAD	CONDITION AT LAST VISIT		NO. ALIVE AND WELL AT 5 YR.	PER CENT ALIVE AND WELL AT 5 YR.
			WELL	POOR		
Total number of cases seen in <i>Bellevue Hospital</i>	396				46	9.3
Exclusion of 120 cases transferred to City Cancer Institute <i>Patients treated in Bellevue Hospital</i>	276	130	36	64	46	16.6
Omitting 23 patients radiated previously elsewhere <i>Primary Bellevue Cases</i>	253	118	34	57	44	18.2
Omitting 9 patients operated upon previously elsewhere <i>Primary Bellevue Cases</i>	244	112	33	55	43	18.6
Omitting 107 patients in which therapy was not completed <i>Bellevue Patients Completely Treated</i>	137	112	33	55	43	33.1

The charted results shown in Table II reveal the fact that the total number of patients known to be alive five years or more was 46. When all cases are included, then the five-year salvage rate is 16.6 per cent, but if deduction is made of the 23 patients who were treated elsewhere with radium or x-rays, of the 9 patients who had a hysterectomy prior to admission to our service, and of the 107 who never returned to complete their course of therapy, then the five-year salvage rate rises to 33.1 per cent. Of the excluded cases, two that were treated elsewhere and one following hysterectomy are alive five or more years following therapy in our clinic.

Table II illustrates the special problems faced by a city hospital cancer clinic in the treatment of cases and in the accurate presentation of end results in a form comparable with those of the private institutions which receive principally primary cases. It shows also how the actual figure to be reported for the absolute cure rate will vary from 9 to 33 per cent, depending on the initial acceptance or rejection of certain groups of hopeless cases from the tabulations.

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LATENT GONORRHEA IN OBSTETRIC PATIENTS

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THE gonococcus has long been identified as an etiologic factor in puerperal morbidity and the syndrome of second-week fever associated with lower abdominal pain and considerable general reaction has been recognized as characteristic of this type of puerperal infection. It has also been appreciated that certain women who harbor gonococci even during the last month of pregnancy suffer no such complication, but the true extent of such silent infections could not be demonstrated. Recently improved cultural techniques offer the opportunity to approximate more closely the true frequency of latent gonorrheal infections. This report is concerned with an investigation by modern bacteriologic methods of the vaginal flora of a consecutive series of patients admitted to the University Hospitals for delivery.

MATERIAL

The series included 500 unselected women admitted in the last two months of gestation for delivery and post-partum care. Among this group, 431 (86.2 per cent) were married, while 69 (13.8 per cent) were single (50), divorced (8), separated

(9), or widowed (2). Two hundred and thirty-three (46.6 per cent) were pregnant for the first time, and the remaining 267 had had from 1 to 14 previous children (average, four plus), and 83 gave histories of previous miscarriages.

TECHNIQUES

At the admission ante-partum examination, usually within twenty-four hours after entrance, the cervix was exposed through a sterile speculum. Swab cultures were taken from the canal and from the posterior vaginal fornix for: (a) gonococci, (b) monilia, and (c) trichomonads, and treated as described below. Spreads were made from both areas on clean microscopic slides. Blood was drawn for the gonococcus complement fixation test as well as for the serologic tests for syphilis. A search was made for stigmas of gonorrhea and a careful history was taken to elicit evidence of previous gonococcal infection. This portion of the study was carried out by one individual (W. W. T.) who also examined the stained spreads.

Identification of Gonococci.—Following the recommendations of Carpenter,¹ one swab from each area was placed immediately in Douglas broth (1.0 c.c.) and transported to the laboratory where it was rubbed over the surface of a chocolate-agar plate (Douglas agar with 5 per cent sheep's blood). One drop of the Douglas broth suspension was also pipetted onto the surface of a second chocolate-agar plate and spread uniformly over the medium with a sterile glass spatula. Thus, two plates were inoculated with material from the cervix and two from the posterior vaginal fornix. (Isolation of the gonococcus was readily achieved from the first plate when the flora was scanty, but was more easily carried out from the second plate when the bacterial growth was plentiful and mixed.)

The inoculated plates were sealed and incubated for forty-eight hours at 37° C. in special jars in which the carbon dioxide content was increased to approximately 12 per cent. At the end of this period the plates were examined for typical colonies.*

If none was seen, the surface of the agar was flushed with a few drops of a 1 per cent aqueous solution of dimethyl paraphenylene diamine hydrochloride† which within a few seconds turns gonococcus colonies red and later black. The organisms can be successfully subcultured while the colonies are red but die during the development of the black discoloration. This color reaction is known as the "oxydase test" and organisms which react are "oxydase positive."

All "oxydase positive" colonies were subcultured on chocolate-agar plates. After incubation for forty-eight hours, smears were made and stained by the Gram method. When examination revealed gram-negative diplococci, pure cultures of these organisms were obtained and inoculated onto glucose, maltose, sucrose, and lactose ascitic fluid agar slants containing Andrade's indicator. The gonococcus ferments only glucose with the formation of acid.

It should be emphasized that "oxydase positive" colonies are not always gonococci. Approximately 1 per cent of the plates presented suggestive colonies which gave a strong positive oxydase reaction but were not gonococci. Three types of such confusing organisms were encountered: a gram-positive diplococcus, a gram-negative staphylococcus, and a gram-negative diplococcobacillus, which was very confusing in the primary plate but in pure culture produced a mucoid glistening growth quite unlike the gonococcus. This last organism is similar in form and pleomorphic tendencies to that described by Thompson,² but apparently differs in its inability to ferment the commonly employed differential sugar media. These three organisms are as yet unidentified but are being subjected to further study.

The spreads were stained by the Gram technique (Holman modification) and examined under the oil immersion objective for definite intracellular gram-negative diplococci.

*Well isolated colonies are from 1 to 3 mm. in diameter with slightly undulated margins and are convex. By transmitted light they are transparent and almost invisible, while they appear grayish and somewhat opaque when viewed from the side.

†Sold by the Eastman Kodak Company as p-Amino dimethyl aniline monohydrochloride.

Identification of Monilia.—The broth swab used to inoculate the first chocolate-agar plate was rubbed over the surface of a fresh moist Sabouraud's slant, which was then incubated at 37° C. for forty-eight hours, when smears were made from visible growths and stained by the Gram technique. The presence of large gram-positive, ovoid budding forms gave presumptive evidence of the presence of monilia. All positive cultures were re-examined after some weeks for mycelia and for ascospores (monilia do not form the latter structures). Although it is recognized that the term "monilia" is controversial, it is used here to designate the yeastlike organisms present in the vagina.

Identification of Trichomonas Vaginalis.—Material from each of the two areas was collected on a swab and inoculated immediately into a 5 per cent solution of human serum in Ringer's solution over a placenta-infusion-agar slant. After twenty-four hours' incubation at 37° C., the liquid was examined for typical motile organisms.

Repeat Cultures and Spreads.—Cultures and spreads were repeated on the eighth or ninth post-partum day immediately before the discharge examination. At first, trichomonas cultures were not made at this time but later the second examination duplicated that on admission.

Serologic Tests.—At the time of the first examination 8 c.c. of blood were drawn for serologic tests for both gonorrhea and syphilis. All of these tests were carried out in the Serologic Division of the State Hygienic Laboratory. The gonococcus complement fixation was performed according to the Kolmer technique using 10 units of Lederle's polyvalent gonococcus antigen. A modified New York complement fixation and the Kline presumptive test were utilized initially for the detection of syphilis and all positive reactors were further tested by the Kahn precipitin and the Kolmer complement fixation procedures.

RESULTS

Gonococcus Cultures.—Among the entire series of 500 patients, the gonococcus was detected by culture in 20 (4.0 per cent). Nineteen yielded the gonococcus before delivery, while cultures from the remaining patient showed "oxydase positive" colonies but a marked overgrowth with *B. proteus* made it impossible to isolate the organism. Fourteen patients were shown to harbor the gonococcus after delivery: among the 6 with no cultural evidence of its presence at this time, 2 had received therapeutic doses of sulfanilamide; in one, technical difficulties probably prevented isolation of the organism; and in the remaining 3 there was no reasonable explanation for the change in findings. None of these 6 culturally negative individuals had positive spreads at either examination. Except in the one patient noted above, the post-partum culture did not show the gonococcus when that taken before delivery had failed to demonstrate its presence. In all the post-partum and in 13 ante-partum patients, there was no disagreement between the results of cultures taken from the cervix and the posterior vaginal fornix; but 6 ante-partum patients presented gonococci in only one area.

Gram-Stained Spreads.—Intracellular organisms fulfilling the staining and morphologic criteria for gonococci were demonstrated in material from both areas in 3 patients before delivery, but not in the remainder, while they were detected among the post-partum group in 12 of the 14 individuals with positive cultures. No definitely positive spreads were found among those patients who were negative on culture, although one case was "suspicious." In this instance, there was no serologic evidence of gonorrhea, but the patient presented an indurated Bartholin's gland.

Gonococcus Complement Fixation.—Among the group proved by culture to harbor the gonococcus, there was 1 "strongly positive," 2 "doubtful," and 17 (85 per cent) "negative" complement fixations. After delivery the "strongly positive" test became "negative." In the control group of 480 patients without cultural evidence of the gonococcus, there were 7 (1.5 per cent) "strongly positive" (1 was repeated and reported "doubtful"), 6 (1.3 per cent) "doubtful" (1 was repeated and reported "negative"), and 460 "negative" tests. Two sera were anticomplementary, and the test was omitted in 5 cases.

Monilia Cultures.—In the ante-partum cultures monilia were grown from 146 patients (29.2 per cent). The fungus was present in 142 (29.7 per cent) of the controls and in 4 (20 per cent) of those with gonococci. It was associated with the trichomonads in 34 instances, including the 4 patients with gonorrhea, while in the remaining 112 individuals no other organism was grown. By contrast, monilia were cultivated only 11 times (2.2 per cent) in the postpartum series.

Trichomonas Vaginalis Cultures.—Trichomonads were cultured either before or after delivery from 113 (23.5 per cent) of the controls and from 7 (35 per cent) of the gonorrheal patients. No figures of relative incidence are available because post-partum cultures were not made in the early cases. Several patients had negative ante-partum but positive post-partum cultures, although in general the results agreed.

Serologic Tests for Syphilis.—There were 13 (2.7 per cent) positive reactors in the control group but none in those with proved gonorrhea.

Clinical Data.—Various clinical data for the 480 controls and for the 20 gonorrheal patients are presented in Table I.

TABLE I. CLINICAL DATA

	CONTROL GROUP (480)		GONORRHEAL GROUP (20)	
	NO.	PER CENT	NO.	PER CENT
Married	423	88.1	8	40.0
Unmarried, divorced, separated, and widowed	57	11.9	12	60.0
No previous pregnancies	225	46.9	8	40.0
One or more previous pregnancies	255	53.1	12	60.0
Average number of previous pregnancies in parous group (255 patients)	4.7		3.3	
History of previous abortions or miscarriages (255 patients)	80	31.4	3	15.0
Evidence of gonorrhea (history or examination)	7	1.5	10	50.0
Abnormal vaginal discharge	86	17.9	11	55.0

Puerperal Course.—Temperatures were recorded every four hours after delivery and the criteria for puerperal morbidity were those suggested by the American Committee on Maternal Welfare. By this standard only two (10 per cent) of the patients with cultural evidence of gonorrhea were "febrile," while in the control group there were 60 (12.5 per cent). In addition there were 6 patients (30 per cent) in the gonorrheal group and 80 (16.7 per cent) of the controls with temperature elevations to 100.4° F. or more which persisted for less than twenty-four hours.

To evaluate the risk involved in performing sterile speculum examinations during late pregnancy, individuals in the control group who were delivered on or before the fourth day after examination were compared with those who were delivered more than fifteen days after the speculum introduction. In the former (135 patients) the morbidity rate was 13.3 per cent as against 13.4 per cent in the latter (127 patients); and the one-day fever incidence was 16.3 and 15.5 per cent, respectively.

The two gonorrheal patients with febrile puerperiums developed their fevers early. One was delivered by low forceps and the other had a manual removal of the placenta. Both patients received sulfanilamide after appearance of the fever and apparently recovered promptly, although in one instance the gonococcus was demonstrated in the second culture. With the thought that the second-week syndrome might have developed after dismissal from the hospital (usually on the ninth or tenth day), follow-up letters were sent to the 20 gonorrheal patients. Replies were received from 15: one reported a "little" lower abdominal pain with urinary frequency, and another was operated upon for "appendicitis" (?) a few weeks after her return home.

The eyes and vaginas of several of the babies of gonorrheal mothers were cultured immediately after birth. Gonococci were demonstrated five times in the eyes but no ophthalmia developed and cultures taken on the eighth or ninth day of life revealed no evidence of the organism. Routine prophylaxis consisted in preliminary flushing of the eyelids with 1:8,000 mercuraphen solution and the instillation of two drops of freshly prepared 1 per cent silver nitrate solution shortly after birth and again three hours later. The vaginas of four babies contained gonococci at birth, but, in spite of the absence of treatment, the organisms were uniformly absent in cultures taken on the eighth or ninth day.

DISCUSSION

It has long been suspected that certain individuals may be gonococcus carriers just as others are carriers for streptococci, pneumococci, meningococci, typhoid bacilli, and other pathogens. By the criteria usually employed, the women in whom the gonococcus was present but who had no clinical evidence of gonorrhea must be viewed as "carriers." In one-half of the group (10 patients) no history or stigmas of the infection could be elicited, while in the remainder the disease had evidently been contracted from six weeks to eight years previous to the first examination. In the older cases, the possibility of reinfection cannot be disregarded although the absence of any exacerbation of symptoms may be significant. Because of the lack of suitable experimental methods, it has been quite impossible to determine whether the gonococcus carrier state is due to increased resistance on the part of the host or to decreased virulence of the organism.

There is considerable evidence to indicate that under certain conditions the susceptibility of different tissues to gonococcal infection may vary from time to time. Newborn babies frequently develop gonorrheal ophthalmia following birth canal inoculations, but rarely, if ever, acquire vaginal infections even though gonococci may be grown from the vaginal introitus as demonstrated in some of the cases here recorded. This lack of susceptibility of the vaginal mucosa evidently represents a local tissue immunity, which is usually related to the character of the mucous membrane or to the acidity of the discharge. Bucura³ in a series of 300 patients found that the titer of the complement fixation factor in blood from the cervix of infected women was higher than that in blood withdrawn from an arm vein, a finding which might be interpreted as indicating an increased local immune reaction in the pelvic structures. Pelouze⁴ has also been prompted to suggest a changing local tissue immunity in explanation of certain clinical facts, such as the apparent increase in susceptibility of the genitourinary tract induced by the ingestion of alcohol, sexual excitement, and menstruation. In the series of "latent" infections here reported, the higher incidence of spreads containing gram-negative intracellular diplococci during the puerperium suggests a local increase in the number of gonococci, whereas the absence of general reactions and of symptoms pointing toward involvement of the tubes and uterus may indicate that the local protective mechanism was adequate to prevent the usual advance of the infection into the upper genital tract.

Certain clinical evidence cited by Thomas and Bayne-Jones,⁵ supports the contention that the gonococcus "may not be pathogenic for all human beings." The lack of susceptibility of laboratory animals to gonococcal infection has so hindered the direct study of possible variations in virulence between different strains of gonococci that other indirect methods of approach have been utilized. Atkin,⁶ and others, have attempted to correlate established clinical virulence, as evidenced by the severity of local and general reactions, with variations in the colony morphology on adequate media. The gonococci grown from acute cases of gonorrhea tend to form large, papilla-bearing colonies, while organisms from chronic cases may produce a preponderance of papilla-free colonies. This investigator has also demonstrated that old laboratory strains more commonly show the papilla-free growths. More recently, Casper⁷ has stressed his belief that "the formation of papilla-free colonies is a sign of degeneration probably due to growth on artificial media," but that by adaptation to human tissues the organism may undergo similar degenerative alterations. This "degeneration" is attributed to loss of an essential carbohydrate which is specific for the particular strain. It is of some interest that in the majority of cultures obtained in the present study the usual colony was smooth and papilla-free or the papilla formation was only slight. In view, however, of the fact that a different medium was employed, definite conclusions will not be drawn pending further study now in progress.

CONCLUSIONS

Among 500 consecutive apparently normal obstetric patients, organisms satisfying the bacteriologic criteria for gonococci were cultivated from the vaginas or cervixes of 20, an incidence of 4 per cent. Although a history suggestive of gonorrhea within eight years could be obtained from 10 of these 20 women, all were without manifestations of active infection at the time the cultures were made and consequently are viewed as "carriers." The puerperal course in these patients was not different from that of a control group.

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Observations on more than five hundred specimens of human semen from 26 different men show that an average ejaculate has a volume of 3.9 c.c., contains 565 million sperms, and requires 3.0 c.c. of N/100 acid to neutralize 1.0 c.c. of the fluid.

HUGO EHRENFEST.

POSTOPERATIVE URETERAL OBSTRUCTION DUE TO PTOSIS OF THE KIDNEY*

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IN A RECENT review of the literature on postoperative ureteral injuries, no reference was found demonstrating complete blockade of the ureter caused by kinking associated with ptosis of the kidney.¹ We are reporting the following case because it demonstrates the importance of considering acute ureteral kink in the differential diagnosis of the causes of postoperative ureteral obstruction.

Mrs. A. P., aged 47 years, was admitted to the hospital March 16, 1939, with a diagnosis of a midline lower abdominal tumor, the approximate size of a twenty to twenty-two weeks' gestation. Her last menstrual period was on Jan. 10, 1939, prior to which time she had menstruated monthly. The past history was negative medically and surgically. There was one full-term pregnancy at the age of 30, which terminated uneventfully. The puerperium was uneventful. General physical examination disclosed no pertinent findings. Rectovaginal abdominal examination revealed a large cystic mass rising out of the pelvis and reaching to the umbilicus. The mass was nontender and freely movable. The uterus was small, firm, and fixed to the right just behind the symphysis pubis by pressure from the tumor. To the left a firm cystic mass approximately 8 by 8 cm. in diameter was felt protruding into the left vaginal fornix. The erythrocyte count was 4,400,000; hemoglobin, 80 per cent (Tallqvist); leucocytes, 8,800; and sedimentation time, seventy minutes. The blood pressure was 66 systolic and 94 diastolic. The urine showed a trace of albumin, but was otherwise negative.

On March 17, 1939, laparotomy was performed. On opening the abdomen a large cystic mass presented itself, filling the entire lower abdominal cavity. The cyst had its origin on the left side and the left Fallopian tube was thinly spread on its upper surface. The left ovary was separately identified and seemed to be replaced by a hard dermoid cyst approximately 5 by 5 cm. in diameter. The large tumor was therefore a huge left intraligamentary cyst. The right ovary was normal. The right broad ligament contained an intraligamentary cyst approximately 4 by 4 cm. in diameter. Because of the bilateral adnexal pathology, and because of the patient's age, a supravaginal hysterectomy and bilateral salpingo-oophorectomy were done, including the parovarian cysts. This was preceded by aspiration of two quarts of clear fluid from the large cyst in order to reduce its size. Patient left the operating room in good condition.

The postoperative course was uneventful until the fifth day when the patient complained of a persistent dull pain on the right side, radiating from the costo-vertebral area anteriorly and downward to the groin. Palpation revealed an enlarged tense kidney, the lower pole of which reached to the level of the iliac crest. This renal swelling was markedly tender, and it was suspected that the enlargement of the kidney may have been due to a right ureteral injury. The urine at this time was negative.

On March 28, 1939, eleven days postoperatively, excretion urography was done (Fig. 1). The roentgenologic report was as follows: "Left kidney normal. The right kidney fails to show concentration, except to a very minor degree in a dilated lower calyx at fifteen minutes and no further function is shown. The right kidney is considerably enlarged in comparison to the opposite side. The

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findings are consistent with a block of the right urinary tract, but whether it is due to a block in the lower ureter or to radiolucent calculi in the pelvis of the kidney cannot be determined. Recommend unilateral retrograde pyelography (right)."



Fig. 1.



Fig. 2.



Fig. 3.

On March 30, 1939, two days later, cystoscopy revealed edema about the right ureteral orifice from which no urine dropped. An ureteral catheter was inserted through the right ureteral orifice for a distance of 15 cm. at which point an impassable obstruction was met. Intravenous injection of indigocarmine was followed by normal excretion on the left side and no excretion on the right side. The diagnosis at this time was occlusion of the right ureter at the approximate level of the infundibulopelvic ligament.

During the subsequent week, the temperature varied from 98.8° to 100.4° F., and the urine was negative except for an occasional leucocyte. The patient improved under conservative management, gained weight, and the kidney mass was apparently slowly receding. The patient was discharged on the eighteenth postoperative day. At home there was continued improvement. The pain subsided, the patient continued to gain weight, and there was a progressive diminution in the size of the "renal mass."

Excretion urography on May 1, 1939 (thirty-four days after cystoscopy), was reported as follows: "The lower pole of the left kidney is at the level of the transverse process of the third lumbar vertebra, and the lower pole of the right kidney is at the level of the upper margin of the fourth lumbar vertebra. The renal pelvis on the right side appears to be larger than on the opposite side and the calyces appear to be slightly blunted (Fig. 2). A film taken with the patient upright reveals the lower pole of the left kidney to have descended to a point opposite the transverse process of the fifth lumbar vertebra, and the lower pole of the right kidney is seen to be at the level of the second sacral vertebra. The distortion of the ureters may be seen on both sides, and particularly on the right side is there noted a marked angulation in the renal pelvis and ureter." (Fig. 3.)

In our opinion the above recorded case and illustrations demonstrate that a ptosed kidney may be held upright by a large pelvic tumor. On removal of the tumor the kidney may drop and the associated acute angulation of the ureter produce findings similar to those which occur with ligation of the ureter. The only other possibility to be considered in this case is the re-establishment of kidney function following the resorption of an encircling catgut ligature. This, however, seems unlikely in view of the work of Caulk² who found that catgut will never absorb before the death of the kidney.

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58 EAST WASHINGTON STREET

VELAMENTOUS INSERTION OF CORD WITH SPONTANEOUS RUPTURE OF VASA PREVIA IN TWIN PREGNANCY*

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VELAMENTOUS insertion of the umbilical cord is an unusual finding in the routine examination of the placenta. It has no clinical significance unless the vessels of the cord are so situated that they are either torn or compressed during labor. Such accidents are more likely to occur when the vessels are located in the lower uterine segment, the so-called vasa previa, but Kosmak reported a case in which rupture of a velamentous cord in the vicinity of the fundus of the uterus occurred.

The incidence of velamentous insertion of the cord is variously given as occurring in about 1 per cent of cases. Williams found it in 1.25 per cent of his cases and quoted Lefèvre who cited an incidence of 0.84 per cent in 15,891 placentas examined. This anomaly is nine times more frequent in twins, and DeLee states that it is almost routine in triplets. A study of the available

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literature showed that vasa previa is very often associated with intra-partum death of the fetus. In most of the cases reported, a diagnosis was not made until the fetus was in very poor condition, hence the treatment was usually unsatisfactory.

The etiology is not fully understood, but the explanation of Franque is considered the most acceptable theory: that the abdominal pedicle ordinarily extends from the fetus to the most vascular portion of the chorion. This is usually in contact with the decidua basalis and therefore the cord becomes inserted into the placenta. Sometimes, early in pregnancy, the most vascular portion of the chorion is the decidua capsularis; hence the abdominal pedicle will become attached to this unusual location. With the continuation of pregnancy, there will be a shift of vascularization to the decidua basalis, but the abdominal pedicle, retaining its original position thus produces a velamentous insertion of the cord. The following case is reported because of its many unusual features:

The patient, aged 20 years, a primipara, was first seen on June 14, 1937, at which time examination revealed a pregnancy of about thirty-two weeks' duration. The last menstrual period occurred on Dec. 27, 1936, and the probable conception date of Jan. 2, 1937, was given. Life was felt on May 9, 1937, and from the menstrual data, term was estimated at Oct. 4, 1937. The size of the abdomen was out of proportion to the estimated duration of the pregnancy, and twins were diagnosed; an x-ray examination corroborated the clinical findings. The prenatal course was uneventful until Aug. 24, 1937, when urinalysis revealed three-plus albumin with many pus cells in the sediment; the blood pressure was 122/76. The blood pressure rose steadily to 148/90 during the following two weeks, and the albuminuria persisted with the additional finding of finely granular casts. The patient was treated conservatively, viz: bed rest, salt-free diet, and magnesium sulphate by mouth. Because she failed to respond to this medical management of her toxemia, induction of labor was instituted by the administration of castor oil, soapsuds enema, and 5 gr. of quinine sulphate. This procedure was not successful until repeated twice in a period of seven days. The membranes ruptured shortly after uterine contractions began, and coincident with the spontaneous rupture of the bag of waters, there was a sudden gush of about one pint of dark red blood followed by a steady trickle of blood resembling the "show." Abdominal palpation at this time revealed that the twins were both in cephalic presentation, and the head of the first fetus was deeply engaged. The fetal heart tones over each fetus were believed to be satisfactory. Rectal palpation twenty-five minutes after the onset of labor found one head on the pelvic floor and the cervix effaced and 5 cm. dilated. The patient was watched closely; soon she began to bear down spontaneously. Since the vaginal bleeding had diminished, the maternal pulse was 80, and the fetal heart tones of both babies appeared to be of good quality, we decided to permit the patient to deliver spontaneously. However, when no progress was noted forty-five minutes after the onset of the second stage, a mediolateral episiotomy was performed and low forceps were applied to the head in a right occipitoanterior position, and delivery of the head was easily effected. A pulseless thin cord was found once around the neck; the cord was cut between two clamps and the first twin, a boy weighing 5 pounds, 5 ounces, was extracted. The baby showed no signs of life and failed to respond to tracheal catheterization, application of external warmth, and intracardiac administration of adrenalin solution. The fetal heart tones of the second twin were good, and since there was no further bleeding, the delivery was delayed in order that the overdistended uterus be given time to retract. The second bag of waters was ruptured artificially fifteen minutes later and the baby delivered after manual rotation of the head from a left occipitoposterior position and the application of low forceps. The second male infant cried spontaneously and seemed vigorous; it weighed 5 pounds, 12 ounces. The placenta was delivered by early expression and was followed by a post-partum hemorrhage estimated at about 750 c.c. of blood. The uterus was promptly packed

and the episiotomy repaired; although the mother's condition was only fair, she responded well to the administration of 1,000 c.c. of 10 per cent glucose solution intravenously.

Inspection of the placenta proved very interesting. It was a single large placenta, weighing 950 gm.; the membranes were composed of two amnions and but a single chorion, typical of monochorial twins. The cord of the first twin was inserted into the membranes in the lower uterine segment as a velamentous insertion. The original rupture of the membranes extended into and perforated a large blood vessel branch of this velamentous inserted cord (see Fig. 1).

This case is of interest chiefly because of the difficulties in diagnosis. Vasa previa is seldom diagnosed before delivery because of its rarity, and the possibility of its occurrence is rarely considered. Very few cases reported in the literature were diagnosed before delivery and the subsequent examination of the placenta. Because of intra-partum bleeding the condition is usually confused with premature separation or placenta previa. The underlying toxemia led us to believe that we were dealing with a mild case of premature separation of the placenta. Vasa previa should be considered whenever bleeding occurs at the time of rupture of the membranes, associated with a well-engaged presenting part, especially when a multiple pregnancy exists. Diagnosis may even be made before rupture of the membranes, if on vaginal examination pulsating vessels are

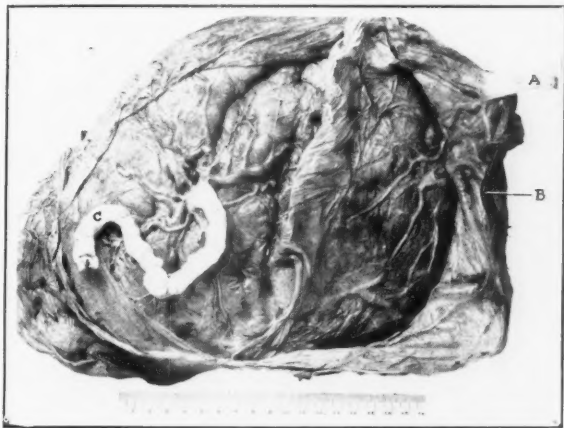


Fig. 1.—Placenta, velamentous insertion of cord of first twin (A), showing vasa previa ruptured (B), cord of second twin centrally inserted (C).

palpated in the membranes. Frommolt and Terasvuori described cases of bleeding prior to rupture of the membranes with intra-partum death of the fetus. In our case, the intra-partum bleeding had occurred from a ruptured branch of an umbilical artery on the maternal surface of the membranes.

The treatment is usually very unsatisfactory since the diagnosis of vasa previa is almost never made before actual rupture of an umbilical vessel occurs; after rupture, the fetus rapidly bleeds to death. When such bleeding occurs, the fetus shows signs of distress and heart tones rapidly fail. In our case, the detection of good heart tones in two locations led us into a false sense of security. Undoubtedly, we were eliciting the heart tones of the second and normal baby in two distinct regions of the abdomen.

In the case of monochorial twins, both may die from exsanguination following rupture of but a single vessel. The second twin showed no sign of asphyxiation or exsanguination; therefore, one may assume either that the loss of blood was insufficient to affect the more vigorous twin or that little or no collateral circulation existed between the two halves of the placenta. The occurrence of post-partum hemorrhage in this case in all likelihood was due to the rapid labor and the overdistention of the uterus in a twin pregnancy.

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185 NORTH WABASH AVENUE
310 SOUTH MICHIGAN AVENUE

TUBERCULOSIS OF THE PLACENTA

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TUBERCULOSIS of the placenta is an infrequent occurrence. Williams¹ had never seen a case in the several thousand placentas he examined at Johns Hopkins Hospital. In 1922, Whitman and Greene² collected 44 cases from the literature in which both tubercles and tubercle bacilli were demonstrable in the placenta. There have been no other cases reported in the American literature since their paper appeared. In 150 consecutive placentas of tuberculous women examined at Sea View Hospital, there was only one case of placental tuberculosis.

The following is the report of a case of tuberculosis of placenta in which both a tuberculous focus and acid-fast bacilli within the focus were demonstrated and in which both mother and infant have been followed for two and one-half years.

A. G., a 29-year-old, colored housewife, was admitted to Sea View Hospital in June, 1936. She had had three normal, full-term pregnancies in 1932, 1934, and 1935. Her first infant died at the age of two years of meningitis. The other two children are living and well. The onset of her tuberculosis was in November, 1935, with cough and expectoration. Pulmonary tuberculosis and pregnancy were diagnosed by the Health Department Clinic, and she was sent to Bellevue Hospital. She was transferred to Riverside Sanatorium in January, 1936, where she received a left initial pneumothorax in May, 1936. Refills were given twice weekly, and she was sent to Sea View Hospital in June, 1936. Here her pulmonary lesion was diagnosed as caseous-pneumonic tuberculosis of the left lung and exudative disease in the right upper lung. Her sputum was Gaffky X before delivery. She delivered spontaneously after an eight hour labor in September, 1936. The infant showed no abnormalities and was immediately removed to a nontuberculous ward. Following delivery the mother received refills. She is still at Sea View Hospital and has been scheduled for thoracoplasty. Her pelvic examination is entirely negative.

The infant was watched carefully. The neonatal period was normal except for cyanosis during the first month. He was always plump and robust but had miliaria and mild rickets, from which he recovered. Repeated x-rays of the lungs, gastric analyses for tubercle bacilli and the Mantoux test up to 1 mg., were all negative. The infant was transferred to The New York Foundling Home in September, 1937, and is there at the present time. He is in good condition and shows no evidence of tuberculosis.

Gross examination of the placenta revealed a yellow area about 7 mm. in diameter. The placenta was otherwise not remarkable. Microscopic sections through this area (Fig. 1) showed an irregular oval area composed of pink granular material with fine nuclear fragments. This area is surrounded by a narrow reticulum of capillaries, fibrils and histiocytes. There are irregular projections into this granular area on one of which are intact polymorphonuclear leucocytes and round cells. There are a number of thin-walled blood vessels in and adjacent to the granular area. Acid-fast bacilli were described in the Ziehl-Neelsen stain.

Before making a diagnosis of placental tuberculosis both tubercle bacilli and tuberculous changes should be demonstrated in the placenta. Using these criteria, only 44 cases have been reported in the literature up to 1922. No cases have been reported in the American literature since that date. Although a rare finding, the importance of placental tuberculosis cannot be over-emphasized. In the clinically unsuspected case of tuberculosis, the finding of tuberculosis of the placenta is evidence of a hematogenous tuberculosis in the mother. Every effort should be made to find the focus of infection which may be in the lungs, in the bronchus, in the



Fig. 1.—Photomicrograph of the placenta which shows an area of necrosis (a) in which acid-fast bacilli were found. Surrounding the area of caseation is a narrow zone of tuberculous granulation tissue (b). The normal placental tissue (c) is present beyond the zone of tuberculous granulation tissue.

skeletal system, in the genitourinary tract or in the gastrointestinal tract. One cannot make a definite statement as to the frequency of placental tuberculosis from the one case described above. Since only several sections of the placenta are examined microscopically, it is a simple matter to miss a small tuberculous focus. Schmorl³ stated that he had to make over two thousand sections of a placenta before demonstrating tuberculosis in one case. Perhaps some method of culturing the entire placenta would yield a higher percentage of positive results.

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TUBAL PREGNANCY WITH TUBERCULOUS SALPINGITIS*

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J. R., A MEXICAN woman (Case C55288), aged 29 years, married eight years, nulliparous, was admitted to the hospital as an emergency on Feb. 16, 1939, because of vaginal bleeding and severe lower abdominal pain. Menses started at 13 years of age, were regular, of the twenty-eight-day type, from 4 to 6 days' duration, scant and without pain, last period Nov. 22, 1938. Although the patient had never used contraceptives, no pregnancies had occurred in the eight years of marriage.

For the past six weeks she had suffered attacks of severe abdominal pain accompanied by bleeding. In the past week, the pain had been more severe and had occurred daily; the flow had been more or less continuous but scanty. The pain was intensified by emptying the bladder and rectum. Except for frequent colds, the past history was negligible. Although she had been under observation at the Municipal Tuberculosis Sanatorium as a contact (one sister had tuberculosis), no diagnosis had been established.

Examination revealed a short, stout woman who was quite pale and in severe pain. During the examination, repeated coughing appeared to aggravate her abdominal pain and also led her to complain of pain in the right shoulder. Examination of the chest revealed no findings. The breasts were hypertrophied and the areolae pigmented. The abdomen was soft in the upper portion but rigid below. There was marked tenderness throughout the hypogastrium. Vagino-abdominal examination revealed a nulliparous cervix which was felt high up near the symphysis, behind which was a definitely bulging cul-de-sac. The mass appeared to fill the true and false pelvis, obliterating the touch for uterus and adnexa. The external os was closed and a blood-stained discharge followed the vaginal examination. Upon percussion, the lower abdomen was *flat*. Temperature was 100.8° to 101° F. (R.); pulse, 92-100; and respirations, 24; the white blood count was 12,800; hemoglobin, 45 per cent; red blood count, 1,140,000; the Kahn test was negative; blood pressure was 106/64.

The diagnosis of ectopic pregnancy which was made was quite obvious, with a large hematocele and probable presence of clots, indicating slow intraperitoneal bleeding for some time previously. The diagnosis was further substantiated by the presence of marked anemia and the absence of shock.

After administration of 1,000 c.c. of 5 per cent glucose in saline by venoclysis, laparotomy was performed under cyclopropane-oxygen anesthesia. Upon opening the peritoneal cavity, a large amount of blood and old dark clots was found, and upon removing the latter, a well-formed fetus, 5 cm. in length, and a placenta, 8 cm. in diameter, were found in the right iliac fossa. The placenta was loosely attached to the omentum but entirely free of the right tube, near which it was found. The right tube and ovary were firmly matted together by dense fibrous adhesions and were adherent to the posterior surface of the broad ligament. The fimbriated end of the tube and ampulla were greatly dilated and actively bleeding. Right salpingo-oophorectomy was done. The left adnexa were likewise bound down, but the ovary was less extensively involved. The tube was thick and spindle-shaped in the ampullar region, with a constricted but patent fimbriated end. The tube was removed, but the uterus, which was normal in size, and the ovary were left in situ. A postoperative diagnosis of tubal abortion with extensive intraperitoneal hemorrhage was made. After closing the abdomen, 500 c.c. of whole blood was transfused by the direct method. During the operation, the pulse slowed from 100 to 80, and respirations dropped from 24 to 18 per minute.

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The pathologic report revealed a *tubal pregnancy with tuberculous salpingitis*. *Pathologic Diagnosis:* Fetus, Placenta, Tube and Ovary: The specimen consisted of multiple fragments of tissue of a variable consistency, comprising a fetus, which, reconstructed, measured 5 cm., a mass of spongy pinkish purple tissue, and a saccular structure, measuring 8 cm. in circumference, the concave aspect of which was granular, trabeculated, and hemorrhagic, and measured 0.8 cm. in thickness. Another specimen consisted of thickened, somewhat dilated segments of Fallopian tube, measuring 8 cm. in length. To this was adherent hemorrhagically discolored fat tissue.

The distal end of the tube was sealed. In the mesosalpinx was an oval structure (ovary) which measured 3 by 1.5 cm. in the greatest dimensions. Its sectioned surface was grayish white, glistening, with minute yellow and larger grayish-white dots. A third specimen consisted of a cord of fat tissue to which was applied dark, brownish red material which resembled clotted blood. Also present was a partially open and sectioned, thin, tubular structure, measuring 6 cm. in length. Adherent to its external surface was a crust of brownish red material.



Fig. 1.

Fig. 1.—Tuberculous salpingitis, seat of tubal abortion (magnification, $\times 100$).

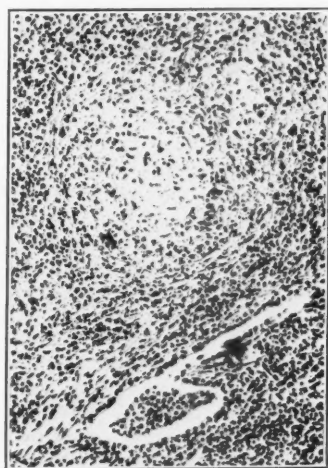


Fig. 2.

Fig. 2.—Tuberculous salpingitis (magnification, $\times 110$).

Histologic Description of the Tube.—The Fallopian tube was diffusely infiltrated with lymphocytes, polymorphonuclear leucocytes and occasional endothelial cells. Scattered throughout were also discrete concentric masses of cells which were fairly well demarcated from the adjacent tissues. These cells were for the most part somewhat elongated, had pale vesicular nuclei and resembled epithelioid cells. Frequently in the center of such a nest of cells a multinucleated giant cell with nuclei arranged about the periphery of the cell was seen. This mass of cells was surrounded by a zone of lymphocytes intermingled with which were occasional large mononuclear leucocytes. Areas of necrosis were found throughout the sections. In some of the sections, adherent to necrotic structureless masses of tissue in which were many extravasated red blood cells, typical chorionic villi were recognizable.

Report of Endometrial Biopsy Specimen.—Throughout the endometrium were seen many accumulations of cells similar to those described in the Fallopian tube. These were arranged to form typical tubercles composed of epithelioid cells, multinucleated giant cells and lymphocytes. In some portions adjacent tubercles had fused forming larger conglomerate tubercles. Areas of necrosis were seen throughout.

The first 6 postoperative days were febrile and characterized by coughing, but convalescence was otherwise satisfactory. No pulmonary lesions were found upon repeated chest examinations by medical and tuberculosis consultants; likewise, x-rays of the chest, sputum examinations, and blood cultures were all negative. On the sixteenth day, hemoglobin was 60 per cent; red blood count, 3,200,000; white blood count, 8,200; temperature, pulse, and respiration, normal. The patient was discharged from the hospital on the twentieth postoperative day.

Follow-up in the clinic one month after operation revealed a good primary union of the abdominal incision; convalescence was satisfactory. Endometrial biopsy (made by Dr. Tulsky in the course of research) revealed tuberculous endometritis. It is planned to continue the follow-up of this patient with oxyperitoneum.

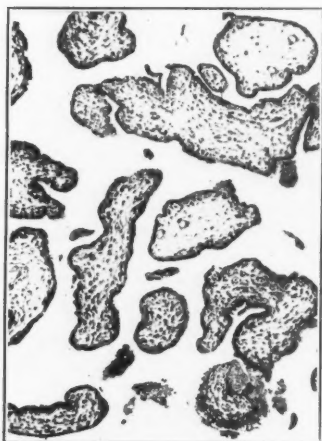


Fig. 3.

Fig. 3.—Placental tissue lying free in the peritoneal cavity (magnification, $\times 56$).

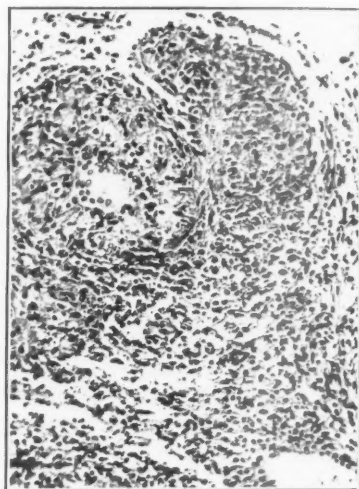


Fig. 4.

Fig. 4.—Endometrial biopsy, tuberculous endometritis (magnification, $\times 140$).

In this case, tuberculosis of the genitalia apparently existed for some time but produced no symptoms of the disease. The menses were regular and there was no pain. The only possible hint of genital disturbance was the long period of sterility. She was a tuberculous contact, one sister being under treatment; however, no pulmonary involvement was found either before or after operation in this patient.

Tubal pregnancy is a very rare complication of tuberculous salpingitis as was recently brought out by Stevenson and Wharton.¹ According to these investigators, only 8 cases previous to theirs have been reported in the medical literature. Furthermore, in the forty-seven years of the existence of the Johns Hopkins' Gynecological Pathology Laboratory, there were 402 cases of tuberculous salpingitis and 516 of tubal pregnancy recorded without a single instance in which the two conditions were combined. Stevenson and Wharton report one such case and discuss the condition in full. Our case, which closely resembles theirs in many respects, is the tenth to be reported in the medical literature of tubal pregnancy associated with tuberculous salpingitis. In addition, a tuberculous endometritis was demonstrated by endometrial biopsy.

REFERENCE

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PRIMARY CHORIONEPITHELIOMA OF THE FALLOPIAN TUBE

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CHORIONEPITHELIOMA of the Fallopian tube is a condition which occurs very infrequently. Recently the thirty-fifth case was reported by R. L. Pearse and C. K. Fraser.* Since their article furnishes a complete bibliography and reviews the literature to the present time, only a simple case report will be presented.

On July 19, 1938, Mrs. G. C., aged 45 years, entered St. Anne's Hospital complaining of pelvic pain associated with a sensation of pressure. The pain was constant, dull, aching in type, located in the lumbrosacral region, and had been present for five years. Her menstrual periods had been abnormal also for the past five years characterized by a fourteen-day cycle with profuse bleeding. In the six months prior to entrance she had lost nine pounds in weight.

Past history disclosed that she was married when nineteen years of age. One year later her first child was born with no abnormalities in the labor, delivery, or puerperium. No past history of ectopic gestation, suggestive or otherwise, was obtained. She had no abortions either spontaneous or induced. During 1923 a whitish vaginal discharge had been present for a few months and then subsided spontaneously.

Complaints referable to the pulmonary system were not elicited except for a few previous attacks of laryngitis during the winter months.

Examination revealed a fairly well-nourished and well-developed white female. Temperature, 98.6° F.; pulse, 84; respiration, 16; blood pressure, 136/78. All findings including examination of the chest were essentially negative except for the pelvic examination.

Pelvic examination revealed a uterus the size of a three months' pregnancy which was distinctly nodular and firm. In the right adnexa was an elongated mass definitely distinct from the body of the uterus. The preoperative impression was myofibromas of the uterus with an associated right adnexal mass, possibly an ectopic pregnancy.

Laboratory findings were as follows: hemoglobin, 80 per cent; erythrocyte count, 4,070,000; leucocytes, 6,000; differential, normal. The urine was negative and the Aschheim-Zondek test was begun on July 19, 1938, because of the possibility of an ectopic pregnancy. Three days later it was returned positive, but by this time the surgery had been performed.

Operation was performed on July 20, 1938. A midline suprapubic incision was made. The mass in the right tube was seen to be about the size of an orange and occupied the middle and distal portion of the tube. It was adherent to the cecum but these adhesions were easily separated. The tumor was removed intact. Both ovaries were moderately atrophic. The left tube was apparently normal. There was no glandular involvement in the pelvic region.

The uterus was well above the symphysis and contained several subserous and intramural fibroids. Supracervical hysterectomy with bilateral salpingo-oophorectomy was performed and the abdomen closed without drainage.

The pathologic report of the specimen described above showed uterine fibroids, the largest was 3.5 cm. in diameter. The tubal tumor grossly was a separate

*AM. J. OBST. & GYNEC. 35: 1046, 1938.

roughly oval mass (9 by 7 by 4.5 cm.). The surface was smooth with small protruding nodules. The cut surface was rough, yellowish pink in color and spongy in consistency. There were conspicuous trabeculae separating the spongy tissue into rounded areas. The microscopic sections of the tumor of the tube were those of a highly malignant tumor of the chorionepithelioma type.

The postoperative course was uneventful until the seventh day, when there was a trace of blood in the sputum. An x-ray of the chest was as follows: "Examination of the chest shows a circumscribed opacity in the region of the left hilus. There is also a cloudiness in the lower left lung field. In view of the patient's history these changes are very suggestive of metastases. However it would be advisable to re-examine the patient after a short interval."

X-ray therapy was begun at this time. Daily treatments over the anterior chest from July 8, 1938, to Aug. 13, 1938, were given, consisting of 171 roentgen units, 200 kilovolts, 25 milliamperes, $\frac{1}{2}$ copper filter, 50 cm. distance, and a 20 cm. field for three minutes.

On the eleventh postoperative day the sutures were removed and the patient was allowed to use the back rest. On the twelfth day very labored respirations with air hunger occurred accompanied by considerable bloody expectoration. This condition recurred several times at subsequent intervals. On the nineteenth day the second chest x-ray showed the following changes: "Examination of the chest shows the circumscribed shadow about the left hilus to be slightly more pronounced than at the last examination. In addition, there are definite soft circumscribed shadows in the lower left lung field. The right hilus shadow is also prominent but no definite changes can be seen in the remaining portions of the previous impression of metastases."

On the twenty-fourth postoperative day (Aug. 13, 1938), the patient suddenly became very dyspneic and died in spite of the usual emergency methods of treatment. Autopsy was not permitted.

COMMENT

The case reported illustrates the difficulty in diagnosis and the highly malignant nature of chorionepithelioma. This patient was particularly interesting because of the absence of any symptoms indicating a previous ectopic pregnancy and the short interval between the operation and the metastases to the lungs.

Page, Seager and Ward: The Use of Placental Blood for Transfusion, *Lancet* 1: 200, 1939.

The authors' experience with placental blood for use in transfusions has been satisfactory. Careful collection is necessary to insure sterility; 1 gm. of sodium citrate in 80 c.c. of twice distilled water is used as an anticoagulant. The third stage of labor is not prolonged by draining the placenta. Blood counts taken on the first, second, seventh, and fourteenth days of life in 12 infants showed no appreciable difference from those in 12 control infants. Mild icterus developed in 2 of the controls and in 1 of the placental group. The average yield of blood was 80 c.c. Placental blood of the same groups may be mixed to provide for a large transfusion. Reactions are not increased by using placental blood. It is stored at 33 to 38° F. and should not be heated before use. The flask is allowed to stand at room temperature one-half hour before use and if the drip method is used, this is unnecessary.

CARL P. HUBER.

CARCINOMA OF FUNDUS IN COMPLETE PROCIDENTIA

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CARCINOMA of fundus in complete procidentia is extremely rare. There are only 5 proved cases reported in the literature, and 3 doubtful cases which might have been carcinomatous at the time an interposition operation was done two or three years previous to the discovery of the malignancy.

Scheffey¹ from the Jefferson Medical College Hospital in 1934 reported 2 cases of adenocarcinoma of the uterus associated with complete procidentia. Two cases are mentioned by Guthrie and Bache² and one by Bissell.³ Bissell also mentions 2 cases of adenocarcinoma of the uterus three years after interposition for complete prolapse, and a similar case is described by McGlinn,⁴ whose paper Bissell discussed at the fifty-second annual meeting of the American Gynecological Society in 1927.

CASE REPORT

J. G., a 59-year-old white female, was admitted to Cumberland Hospital, on April 22, 1936, complaining of a "dropped womb" of fifteen years' duration.

Fifteen years before she had been told that she had a prolapsed uterus, but she refused operative interference. For the past ten years she had constantly worn a vulvar pad, as the uterus "dropped out" and interfered with walking. For the past two years she had had a marked vaginal discharge, which during the last three months had become sanguineous.

She began to menstruate at the age of 11, each period lasting three days. She had always been "regular." The patient had had three children, two of whom are living, one having died in infancy. Her menopause began nine years ago.

Examination revealed a well-developed, well-nourished female, weighing 174 pounds. Her chest showed evidence of chronic bronchitis. She was a hypertensive cardiac, Class 2B, with a systolic pressure of 240 and diastolic of 130. The abdomen was tympanitic and distended. She had a large cystocele and rectocele. The entire cervix and lower segment of the uterus protruded from the vagina; the cervix was lacerated and dry, having the consistency of parchment. There was no evidence of any bleeding.

The urine showed a trace of albumin. The blood count was within normal limits. The blood Wassermann was negative. The blood chemistry showed: sugar 110 mg., urea 16.7, uric acid 4.3, creatinine 1.6.

Again she was very reluctant to undergo any operation, and was therefore given supportive treatment for her hypertension and cardiac condition, and kept under observation.

Two months later her abdomen became progressively distended and showed evidence of ascites. On July 18, 4,000 c.c. of yellow fluid was removed by abdominal paracentesis. After the removal of the fluid a mass was felt in the right lower quadrant. The uterus was fixed in the pelvis and could not be displaced. She developed a low grade temperature. On August 3, 3,600 c.c. of fluid was removed. She began to lose ground very rapidly and died on August 12.

An autopsy was performed by Dr. Polayes, the pathologist. The final anatomic diagnoses were as follows: (1) Adenocarcinoma of the uterus; (2) metastatic carcinoma of iliac nodes, posterior uterine wall, pouch of Douglas, omentum, rectum, bladder and liver; (3) perforation of rectum; (4) peritonitis

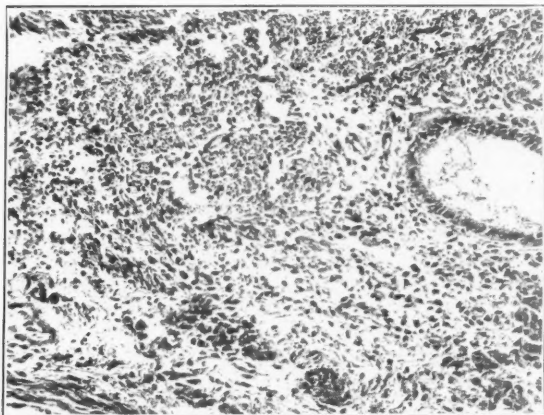


Fig. 1.—Low power photomicrograph ($\times 200$) showing mass of tumor cells invading muscularis.

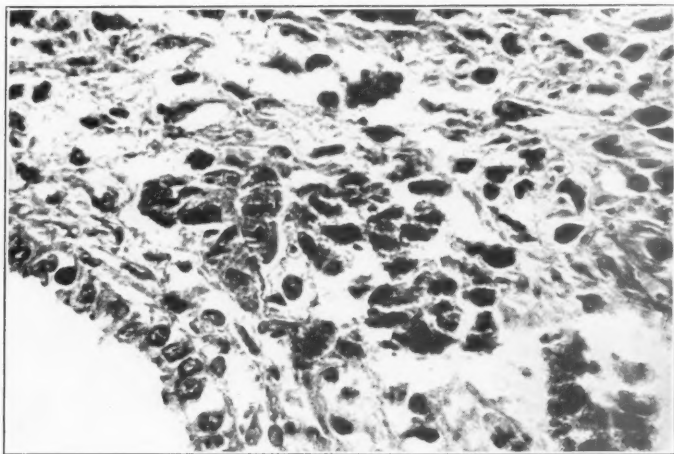


Fig. 2.—High power photomicrograph ($\times 800$) showing anaplastic characteristics of tumor cells.

(*B. coli*); (5) thrombosis of iliac veins; (6) myofibrosis cardiac; (7) pulmonary congestion and edema; (8) congestion of liver and spleen; (9) bilateral chronic salpingitis; (10) diverticulosis coli; (11) renal calcification; and (12) hypertrophic bladder.

Only 5 proved cases of this type are reported in the literature, and one additional case with autopsy findings is here presented.

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RECTAL ADMINISTRATION OF EVIPAL SOLUBLE IN OBSTETRICS*

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IN JUNE, 1936, Gwathmey reported 150 cases in which he had administered evipal soluble rectally as a preanesthetic agent in general surgery.¹ Included within this report were the results of a series of animal experiments performed in the laboratories of the New York University School of Medicine which demonstrated that the therapeutic index (minimal lethal dose divided by the minimal anesthetic dose) for the rectal administration of the drug was 4. This offered an even greater margin of safety than the intravenous use of evipal soluble in which the therapeutic index was determined to be 3.3. The rectal administration of the drug produced satisfactory muscular relaxation and adequate length of action. Gwathmey concluded that the rectal administration of evipal soluble as a preanesthetic agent in surgery was safe, and that the dosage which he employed ("0.02 gram per pound body weight") made inhalation, local, or spinal anesthesia safer for the patient and easier for the doctor.

Evipal soluble has been employed intravenously in obstetrics as an anesthetic agent in both operative and spontaneous deliveries.² For general anesthesia in surgical procedures, evipal soluble has been given intravenously in over 800,000 cases in Europe alone.³

With the background of its successful use rectally and intravenously, it was decided to use evipal soluble rectally as an analgesic agent in obstetrics at this hospital and to evaluate the results. The drug was administered to 75 women in labor and records were kept of the results. Forty-one patients were primigravidas and 34 were multiparas. While the obstetric patients in this hospital average 35 per cent primigravidas and 65 per cent multiparas, many of the multiparous patients entered the hospital far advanced in labor and were unsuitable for the rectal use of evipal.

ADMINISTRATION OF EVIPAL SOLUBLE RECTALLY

The technique of administering the drug is simple. First, the rectum is thoroughly emptied by a cleansing enema. The calculated amount of the solution is then injected into the rectum with a glass syringe, by means of a rubber urethral catheter inserted 4 to 6 inches into the rectum, and preferably above the presenting part. The solution is administered rapidly and is followed by the injection of 10 c.c. of water. The buttocks are pressed closely together for a few minutes and the patient is instructed to avoid straining. In only two instances was there any difficulty in retaining the solution, and in no case was there any evidence of rectal irritation.

*The patients comprising this series were observed in the Los Angeles County General Hospital.

The total dosage employed varied between 1 and 4 gm. per patient. Although most of the women were given 2 gm. of evipal, some of the heavier patients received 3 gm. A second dose of evipal was administered to a few patients. Forty-nine out of the 75 women in the series received no other analgesic drug; 5 received 0.25 gr. of morphine sulfate, and 13 were given $\frac{1}{32}$ gr. of dilaudid thirty to forty-five minutes before the use of the evipal solution. In 5 cases the desired results were not obtained by the use of evipal rectally, and its use was supplemented by the oral administration of pentobarbital sodium. One patient was given 20 c.c. of paraldehyde and 2 were given Gwathmey rectal analgesia in addition to the rectal evipal. As a general rule we gave the rectal evipal when the cervix was dilated 2 to 4 cm. and regular uterine contractions, occurring every three to five minutes and lasting thirty to forty-five seconds, were present. In some instances the drug was given considerably later in labor.

GENERAL EFFECTS FOLLOWING RECTAL INSTILLATION

The effect following the use of evipal rectally was found to be variable. Within a few minutes all patients noted more or less drowsiness. Many slept for from thirty minutes to one hour. During this sleep the respirations were slightly shallow but were unchanged in rate. The pulse remained full and regular and there was no remarkable change in rate, although in most cases a slight increase was noticed. In a few cases flushing of the skin was observed. Blood pressure readings showed no significant alteration.

Uterine contractions were not affected in intensity or frequency, and in the series there was no increase in our usual number of operative deliveries. The average length of labor was 17.3 hours. Considering the number of primiparas, this figure is close to the average length of labor generally observed in this hospital. Contraction of the uterus following delivery is not affected and no unusual bleeding occurred in this series.

The length of effective analgesia proved extremely variable. In one case the effect lasted only fifteen minutes, the patient awakening at the end of that time alert

STATISTICAL DATA

Number of patients in series	75	
Primiparas	41	54.6%
Multiparas	34	45.4%

Dosage of Evipal Soluble Rectal

Smallest total dose	1 gm.	
Largest total dose	4 gm.	
Patients receiving one dose only	66	88%
Patients receiving two doses	9	12%
Patients receiving more than two doses	0	0

Supplementary Drugs Employed

Evipal used alone	49	65.4%
Morphine sulfate and evipal	5	6.7%
Dilaudid and evipal	13	17.3%
Pentobarbital sodium and evipal	5	6.7%
Gwathmey rectal analgesia and evipal	2	2.6%
Paraldehyde and evipal	1	1.3%

Length of Analgesia

Shortest analgesia observed	15 minutes
Longest analgesia observed	6 hours
Average length of analgesia	2 to 2.5 hours

Evaluation of Analgesia Secured

Good results	35	46.6%
Fair results	22	29.4%
Poor results	18	24%
Cooperative patients	44	58.6%
Uncooperative patients	31	41.4%

and complaining to such an extent that it was necessary to use other drugs for the relief of pain. In a few cases relief from pain was secured for from four to six hours; but in general the effect of the drug lasted for two to two and one-half hours. Because of the short duration of effective analgesia by the use of evipal, our best results were obtained in those patients in whom delivery followed within two hours after administration of the drug. Forty-four of the 75 patients were considered reasonably cooperative on the delivery table, while 31 were not. Of this latter group many were wild and completely uncooperative. In 35 instances the analgesia secured was good, in 22 it was considered fair, while in 18 it was considered poor. The amount of amnesia as determined by questioning the patient on the first postpartum day also showed great variation, some patients remembering nothing, others having no amnesia whatsoever. The impression of the authors, and of the interns and nurses who observed these 75 patients, was that the patients were not securing as much relief from pain as was obtained by patients receiving other analgesic agents.

REACTIONS NOTED

Minor Reactions.—In several instances twitching of localized muscle groups was noticed. The upper or lower extremities were usually involved and occasionally the muscles of the face. These were rarely severe. In one case, however, generalized twitchings of all the body muscles were present, severe enough to resemble a convulsion. In another case they resembled a chill. These reactions were of short duration and were not the cause of concern. As the patients dropped off to sleep, they disappeared. The above mild reactions have been generally described in the literature on lival soluble.

Severe Reactions.—Two patients suffered severe reactions which were the cause of extreme concern. These cases are described in detail.

CASE 1.—(532-895.) White, female, aged 24, para ii, gravida iii. Last menstrual period March 15, 1936. Due Dec. 22, 1936. She was admitted to the hospital on Jan. 6, 1937 at 12:30 P.M. She had had two previous full-term pregnancies with spontaneous delivery of 8½ and 9 pound living babies. She had had no prenatal care. Pregnancy was uneventful to full term. Pains began six hours before admittance.

Findings on Admission.—Blood pressure, 132/76; temperature, 98.4° F.; pulse, 80/min.; respiration, 20/min. Examination of heart and lungs essentially normal. There were mild uterine contractions every twenty minutes. Height of fundus, 35 cm. Pelvic measurements were ample. Position L.O.A. Station floating. Cervix uneffaced and dilated 1 cm. Fetal heart tones 136, regular and strong.

Examination of urine was negative for albumin and sugar. Hemoglobin was 13.2 gm. (Sahli).

Progress.—9:00 P.M.: Moderate uterine contractions every ten minutes. Fetal heart tones were 136. Station plus 1. Dilation of cervix 4 cm. Effacement 50 per cent. Two grams of evipal soluble were given rectally at this time.

10:30 P.M.: Dilatation of cervix complete and head on perineum.

The patient was placed on the delivery table and was given 2 ounces of ether by drop method in order to permit draping and to prevent a precipitate delivery. Sudden cyanosis and a drop in respirations to 4 per minute was noticed. The ether mask was removed and carbogen given. The patient was comatose. She was given adrenalin (1-1,000) minims iii, 7½ gr. of caffein-sodio-benzoate, and 1 ampoule of coramine, by hypodermic. The blood pressure was 140/90, pulse rate 100. The skin was cold and clammy. Hot blankets were applied.

At 11:45 P.M., or approximately one hour after the above collapse, the patient regained consciousness. The respiratory rate was then 40/min. Fetal heart tones were 160/min. and regular in rate. Uterine contractions returned, and forty-five minutes later, at 12:15 A.M. a 7 pound 7 ounce baby was delivered spontaneously. No fetal asphyxia was present.

The third stage and further recovery of the patient were uneventful.

CASE 2.—(524-868.) White, female, aged 24, para 0, gravida i. Last menstrual period Jan. 29, 1936. Due Nov. 5, 1936. She was admitted to the hospital on Nov.

11, 1936 at 7:47 P.M. She had had adequate prenatal care at a local clinic. Mild edema of ankles was present for two weeks.

Findings on Admission.—Blood pressure, 130/76; temperature, 99.4° F.; pulse, 94/min.; respiration, 20/min. Examination of heart and lungs essentially normal. Mild uterine contractions present every five minutes. Height of fundus 36 cm. Pelvic measurements ample. Position L.O.A. Station -2 cm. Cervix effaced 40 per cent and dilated 1 cm. Fetal heart tones 148, regular. Urine negative for albumin and sugar.

Progress.—10:00 P.M.: Mild uterine contractions every three minutes. Fetal heart tones 148. Station plus 1. Dilaudid, $\frac{1}{32}$ gr., by hypodermic given at this time. Dilatation cervix 3 to 4 cm.

10:35 P.M.: Two grams of evipal soluble given rectally.

12:00 midnight. Dilatation of cervix complete and head on perineum. At 12:30 A.M. the patient was placed on the delivery table. 50 c.c. of $\frac{1}{2}$ per cent novocaine was infiltrated into the perineum and a left mediolateral episiotomy was done. The patient was then anesthetized, using a total of 3 ounces of ether by drop method, and an easy prophylactic low forceps operation was performed. An 8 pound 7 ounce infant was delivered which was moderately asphyxiated, necessitating tracheal insufflation for a few minutes.

Following delivery, the ether mask was removed. The color of the patient was good and respirations were regular. The patient began to move and seemed to be awakening. The perineal repair had just been started when sudden cyanosis and cessation of respiration was noticed. Traction on the tongue was applied with an Allis clamp and artificial respiration and carbogen were given. Respirations returned after three to five minutes and cyanosis disappeared. Further recovery of the patient was uneventful.

EFFECT ON BABY

The fetal heart rate was not materially affected in any of our cases. Fifty babies in this series cried spontaneously. A delayed cry was noticed in 23 instances. Two babies were stillborn; in 1 case the fetal heart tones had not been heard during labor, while in the other a tentorial tear resulted from a difficult operative delivery. Mild asphyxia in which the babies were resuscitated with no difficulty was noted 17 times. Moderate fetal asphyxia was observed in 7 instances. Three of these mothers had received evipal and dilaudid, 1 had received pentobarbital sodium following evipal, and 3 had received evipal alone. Severe asphyxia in which the babies were resuscitated with difficulty by use of the tracheal catheter was noticed 3 times. Two of these patients had received evipal as the only analgesic agent, while the other had received evipal and dilaudid. The nurses in care of the nursery reported an exaggerated drowsiness of all of the babies in this series during the first day of life.

Babies with spontaneous cry	50	66.7%
Babies with delayed cry	23	30.7%
Babies stillborn	2	2.6%
Mild Asphyxia	17	22.6%
Evipal alone used	10	
Evipal and dilaudid	1	
Evipal and pentobarbital sodium	3	
Moderate Asphyxia	7	9.3%
Evipal alone used	3	
Evipal and dilaudid	3	
Evipal and pentobarbital sodium	1	
Severe Asphyxia	3	4.0%
Evipal alone used	2	
Evipal and dilaudid	1	

SUMMARY

1. Evipal soluble was administered rectally to 75 women in labor and the results were tabulated. The dosage corresponds to that of previous investigators.

2. The analgesia and amnesia secured were extremely variable. The duration of analgesia was generally short, ranging from fifteen minutes to six hours, averaging about two and one-half hours. In some cases amnesia was complete and in others totally absent. Despite the fact that about 35 per cent of the patients received supplementary drugs, the total number of good results was low (46.6 per cent).

3. Two grave maternal reactions were observed. Although both patients recovered, the reactions were very alarming. These two cases are described in detail.

4. Three babies were moderately asphyxiated at birth when evipal was the only analgesic drug used during labor. Two babies in cases in which evipal alone was used during labor exhibited severe asphyxia. All the babies in this series were drowsy for about twenty-four hours following delivery.

CONCLUSION

We believe that evipal soluble in the dosage used is unsuitable for rectal administration as an obstetric analgesic agent.

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MASSIVE DOSES OF SULFANILAMIDE IN PREGNANCY

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THE rapid acceptance of sulfanilamide and its derivatives in the treatment of many types of infection has resulted in a very incomplete literature on many phases of its use. The uses of and contraindications to the drug during pregnancy are one of the phases on which there is very little available literature. Recently Adair has published some experimental work on animals which indicated that the drug has definitely harmful effects on the fetus. And yet occasions will arise when the life of the fetus must be a secondary consideration, and the use of the drug a life-saving measure for the mother. We have encountered such a case, and used massive doses of the drug. We herewith report this case that it may serve as a guide in practically an uncharted field.

Mrs. L. H., para 0, gravida i, white, aged 24 years, was first seen by us on June 21, 1938, in the third month of her pregnancy. Last period March 19, 1938. Physical examination at this time was essentially negative. Pelvic measurements were ample. Kahn test was negative, and the blood count was within normal limits. Her pregnancy was uneventful except for an attack of acute left kidney pain. Pyelogram revealed a double ureter with hydronephrosis on the left.

On or about Nov. 1, 1938, the patient contracted an acute upper respiratory infection which rapidly developed into a paranasitis. She was given local treatment and sulfanilamide by mouth without any apparent benefit. On December 1 she developed bilateral otitis media, and both drums perforated. On December 10 she developed left mastoid tenderness and was admitted to George Washington University Hospital. An x-ray taken on admission showed left maxillary and ethmoid

sinusitis and bilateral mastoiditis with more involvement on the left. A left mastoidectomy was performed at once by Dr. G. B. Tribbe. Following the operation, the patient was given 20 c.c. of prontosil intramuscularly every four hours, a total of 120 c.c. a day. She was also given a transfusion and progesterone, one international unit twice a day, to prevent labor. After two days her condition improved somewhat and the prontosil was cut to 15 c.c. every four hours which she continued to receive for three more days.

Following this therapy, the infection rapidly subsided. Her temperature remained normal after the fifth day. Labor began on Jan. 2, 1939, and she was delivered of a normal full-term infant, weighing 6 pounds, 9 ounces after a four-hour labor. The puerperium was uneventful and she was discharged on Jan. 14, 1939.

There are many cases in which an intercurrent infection may threaten the life of the parturient woman. We feel that in these cases the use of sulfanilamide and its derivatives is justified regardless of the effect on the fetus. Such a case has been presented and many similar cases will probably arise. The use of sulfapyridine in pneumonia during pregnancy offers possibilities of lowering a mortality rate that has varied little in the last decade. Until it is proved that these products are definitely injurious to the fetus, we feel that they should be used whenever indicated if the life of the mother is threatened.

COMBINED INTRA- AND EXTRAUTERINE PREGNANCY

ARTHUR M. ROSENTHAL, M.D., LOS ANGELES, CALIF.

COEXISTING intrauterine and extrauterine pregnancy is not an unusually rare condition. Up until 1913 there were collected and reported 243 cases of combined pregnancies. In 1926 Novak had added 32 more cases, and in 1935 Hefferman summarized the literature, reporting 2 more cases totaling 277. I found 9 additional cases in the recent literature bringing the approximate total of these cases to 286.

The greater number of cases reported did not terminate with a living child, as in the present instance. Uterine abortion before the fourth month usually occurred. A large number of the histories indicated multiple pregnancies in the families.

CASE REPORT

Mrs. R. B., white, aged 28, para i, gravida 0, was seen in consultation on Sept. 3, 1938, complaining of severe lower abdominal cramps associated with spotting of several days' duration. Her past history was essentially negative. There were no previous pregnancies or history of miscarriage. The family history indicated multiple pregnancies. Menstrual history showed a regularity of menses up until July 15, 1938, which was her last menstrual period until the present spotting had appeared. Examination disclosed a healthy appearing woman, not acutely ill, merely complaining of cramplike pains in the lower abdomen. The latter was tender to palpation, with muscular rigidity on the right side. Vaginal examination showed a soft cervix and a brownish bloody discharge. The uterus was slightly increased in size, suggesting an early pregnancy. The right fornix presented a bulbous cystic mass the size of a lemon, intimately connected with the uterus and very tender. A diagnosis of ruptured right tubal pregnancy was made. At operation there were free blood in the peritoneal cavity and large blood clots over the fimbriated end of the bulbous, bluish tube. The uterus was slightly enlarged commensurate with such an early pregnancy. The right tube and appendix were removed. The peritoneal cavity was cleared of all free blood clots and the abdomen closed without drainage. The patient's postoperative course was very mild and she left the hospital on Sept. 14, 1938.

Pathologic Report.—Specimen consisted of an appendix, a Fallopian tube and a mass of blood clot. The Fallopian tube showed delicate fimbriae. The wall was

ruptured near the uterine extremity and the adjacent structures were heavily infiltrated with blood. The muscular wall of the tube showed evidence of recent hemorrhage, in areas there were bits of decidual tissue. There were a number of well-preserved immature chorionic villi which lay within a mass of blood clots.

Two weeks after leaving the hospital, Mrs. R. B. came to the office for examination. At this time her general health was very good except for a complaint of slight morning nausea. Examination disclosed a symmetrically enlarged uterus of about ten weeks' pregnancy which aroused a suspicion of a coexisting uterine pregnancy. This was verified on Oct. 1, 1938 by a positive Aschheim-Zondek reaction.

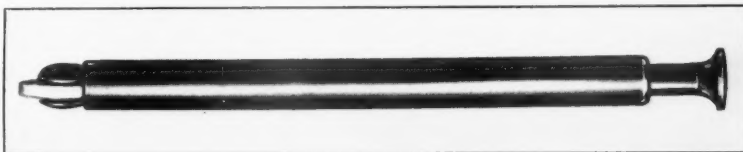
The course of pregnancy was entirely normal, and on May 2, 1939 this patient was delivered of a normal, living, female child.

619 SOUTH BONNIE BRAE STREET

AN INSTRUMENT FOR THE TREATMENT OF TRICHOMONAS VAGINITIS

MILTON ROBINSON, M.D., NEW YORK, N. Y.

IN THE treatment of *Trichomonas vaginalis* vaginitis, as well as in other types of leucorrhea, or vaginitis, the medication prescribed has been compounded into tablets, capsules, or pessaries. The method of introducing these substances into the vagina has been left to the ability of the physician to teach the patient the proper technique and to the ingenuity and physical skill of the patient to follow it. For esthetic reasons many women find the introduction of medication with their fingers into the vaginal tract unpleasant. This is especially so in virgins and nullipara with small introitus. For aseptic reasons one can see that in the attempt to place the medication properly with the finger the tissues may be readily traumatized and infected with organisms which, if not already there, might be introduced by the fingers.



Since it is not always feasible to have the patient return to the office each time for treatment, I have devised a small apparatus, no thicker than the average douche nozzle, seven inches long, of a nonmetallic substance which will grasp any solid form of medication and can be easily introduced into the vagina. The tablet is thus placed high up in the vault, in approximation to the cervix. When this medication has been introduced into the proper place, a spring release is pressed and the instrument is withdrawn. The substance is left in the vagina to mix intimately with the vaginal and cervical secretion, to dissolve, and by gravity flow over the vaginal walls.

The instrument will resist all of the commonly used cold sterilizing solutions (lysol, bichloride, alcohol) and can be used repeatedly over a long period of time without impairing its effectiveness.

The instrument is manufactured by the J. Kriser Corporation, 30 East Tenth St., N. Y.

Society Transactions

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF MAY 19, 1939

The following papers were presented: **The Electrical and Mechanical Activity of the Human Nonpregnant Uterus.** Drs. Edmund Jacobson, Julius E. Lackner and Melvin B. Sinykin (by invitation). (For original article, see page 1008.)

Pelvic Prognosis on the Basis of Recent X-ray Studies of the Female Pelvis. Dr. Everett C. Hartley (by invitation). (For original article, see page 1037.)

Estrin and Progesterone Relationship in Obstetrics and Gynecology. Dr. Phillip F. Schneider (by invitation).

The Clinical Use of Gonadotropic Hormone from Pregnant Mare Serum. Drs. Carl P. Huber (by invitation) and M. Edward Davis.

Postoperative Ureteral Obstruction Due to Ptosis of the Kidney. Drs. M. L. Leventhal and E. M. Solomon. (For original article, see page 1061.)

Velamentous Insertion of Cord with Spontaneous Rupture of Vasa Previa in Twin Pregnancy. Drs. A. J. Kobak and M. R. Cohen. (For original article, see page 1063.)

Tubal Pregnancy with Tuberculous Salpingitis. Dr. I. F. Stein. (For original article, see page 1068.)

BROOKLYN GYNECOLOGICAL SOCIETY

MEETING OF APRIL 14, 1939

The following program was presented:

A Case of Superfetation in Uterus Didelphys. Dr. Irving T. Soifer.

Studies in Artificial Ovulation With the Hormone of Pregnant Mares' Serum. Dr. Samuel L. Siegler and Dr. M. J. Fein. (For original article, see page 1021.)

MEETING OF MAY 5, 1939

The following papers were presented:

Introductory Remarks on the Brooklyn Maternal Mortality for the Year 1938. Dr. M. V. Armstrong.

Mortality in Cesarean Sections. Dr. Frank P. Light.

Anesthetic Deaths in Obstetrics: The Preventable Factors. Dr. A. H. Rosenthal.

Indications for Obstetrical Consultation. Dr. H. S. Acken, Jr.

Preventability and Treatment of Hemorrhage in Obstetrics. Dr. J. A. O'Leary.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Placenta

Loynnnet, R., and Ambre, E.: Severe Hemorrhage Due to Low Insertion of the Ovum in the Early Months of Pregnancy, Rev. franç. de gynéc. et d'obst. 33: 613, 1938.

In a series of 750 pregnancy cases in the Lyon Obstetric Clinic, the authors observed 5 cases of severe hemorrhage in the early months of pregnancy which were due to placenta previa and which necessitated evacuation of the uterus. The authors accept the explanation of Rhenter and Pageaud for this condition, namely that during the fourth month, after the decidua at the internal os is absorbed, chorionic villi become free and lead to bleeding. The treatment of choice in such cases is artificial rupture of the membranes. Usually this is not sufficient to start labor, and oxytocics must be administered. Other measures which may have to be employed are: cervical tamponade, a Champetier de Ribes bag or a Braxton Hicks version.

The prognosis for the mother in these cases is less serious than it is for placenta previa near or at term, but of course the fetus must be sacrificed.

J. P. GREENHILL.

Cetroni, M. P.: Placentography and Radiological Diagnosis of Placenta Previa, Clin. ostet. 39: 373, 1937.

The author summarizes the work already done on placentography. He points out that direct placentography, by injecting intravenously, opaque substance, is impractical since the dose required is lethal.

He states that there are two indirect methods of visualizing the placenta. The first he names "amniotography," which consists of injecting a contrasting liquid in the ovular cavity. The results obtained by this method seemed satisfactory to the author, because in addition to the visualization of the placenta, the contour of the fetus and the cord are also demonstrable. The second method is based on revealing the distance between the fetal head and the urinary bladder which is filled with a contrasting fluid. In cases of placenta previa, this distance is considerably greater.

AUGUST F. DARO.

Jablonski and Meisels: Diagnostic Value of Cystography in Placenta Praevia, Zentralbl. f. Gynäk. 62: 532, 1938.

Observations are reported with the cystographic method which Ude and Urner recommended for the diagnosis of placenta previa. The method is suited especially for the cases in which the fetus is in the vertex position. Ude and Urner maintained that the distance between the lower outline of the fetal cranium and the contrast-shadow of the bladder measures normally at the most 1 cm. and that this distance is taken up by the thickness of the wall of the urinary bladder, of the uterine wall, and of the fetal scalp. Jablonski and Meisels, however, assert that the distance is dependent on (1) the degree of dilatation of the lower uterine

segment and the lifting of the bladder connected with this, and (2) the lowering of the fetal head. This explains why, between the seventh and tenth months of pregnancy, the distance becomes constantly smaller so that during the last weeks of pregnancy the outline of the head almost touches the shadow of the bladder. However, if a body is interposed between the fetal head and the uterine wall, such as for instance the placenta or a myoma, the distance is in excess of 1 cm. The authors made this test on 30 pregnant women. In 16 of them hemorrhages had occurred during the second half of pregnancy and the other 14 cases served as controls. They found that this roentgenologic method permits the detection or exclusion of a placenta previa if it is of the central or lateral type. A placenta previa marginalis, particularly if located on the posterior uterine wall, usually cannot be determined in this manner. Another disadvantage is that the method can be used only if the fetus is in the vertex position. However, the authors suggest that in some cases of oblique, transverse or pelvic position, external version into the vertex position can be tried. They succeeded in accomplishing this in three cases.

J. P. GREENHILL.

Lloyd, O., and Giesen, J. E.: The Treatment of Placenta Praevia, Brit. M. J. 1: 1258, 1938.

At Queen Charlotte's Maternity Hospital a standardized method for treatment of placenta previa is established. A series of 143 cases treated in the past five years is compared with a similar number treated prior to this period. The principles of the treatment consist of (1) proper preparation for examination of the patient per vaginam. This includes blood grouping and preparations for transfusion and for vaginal packing. (2) Vaginal examination under light general anesthesia. A diagnosis was established as to the type of placenta previa present, central, marginal, or lateral.

The central placenta previa was treated by routine cesarean section irrespective of the condition of the fetus. If bleeding follows the vaginal examination, vagina and cervical canal are packed. The patient was given morphine and transfusion prior to operation.

Lateral and marginal placenta previas were treated by simple rupture of the membranes and plugging of the vagina where bleeding ensued. In all cases, blood loss was replaced by early and adequate transfusion.

Podalic version is not advocated, but where a complete breech presentation was present and the os sufficiently dilated, a leg was pulled down to effect pressure by the half breech. Willett's scalp forceps were employed on one or two cases after removal of the packing. Stress is laid on efficient packing of the vagina.

The advantages claimed for packing are that bleeding can be completely arrested, and time gained to restore the patient's general condition; vascular sinuses exposed by placental separation are compressed and clotting can occur; packing of the vagina in conjunction with artificial rupture, though a stimulus to uterine contractions, does not result in unduly rapid delivery.

The results of this treatment show a mortality rate of 1.4 per cent, a morbidity rate of 15.4 per cent, and a stillbirth rate of 53.8 per cent, as compared with the group of 143 patients treated prior to this standard method with a mortality rate of 5.6 per cent, morbidity rate of 14.7 per cent, and stillbirth rate of 50.05 per cent.

Emphasis is laid upon the value of a predetermined routine.

F. L. ADAIR AND S. A. PEARL.

Liepelt, M.: The Best Form of Therapy for Placenta Previa, Arch. f. Gynäk. 167: 52, 1938.

The incidence of placenta previa was 1.69 per cent at the Cologne Frauenklinik during the last decade. Of these cases, 128 were classified as low implantation, 47 as marginal, 102 as lateral, and 121 as central.

Following medical stimulation of labor pains, 89 patients were delivered spontaneously, and 19 were treated by simple rupture of the membranes. Braxton Hicks version was done in 24 and version and extraction in 37. In 18 of the latter, craniotomy was performed on the aftercoming head. Of the 40 patients in whom bags were used, 24 were followed by spontaneous delivery and 16 by version and extraction. The remaining 182 were terminated by cesarean section.

The fetal mortality following cesarean section was 21.5 per cent and the maternal mortality was 6.25 per cent. For the entire series, the fetal mortality was 33.25 per cent and the maternal mortality 6.4 per cent.

The author concludes from his studies that every patient should have a careful vaginal examination for the exact diagnosis of the type of placenta previa and that the examiner must be prepared to terminate immediately the pregnancy if hemorrhage ensues. He recommends Braxton Hicks version as the treatment of choice when the fetus is nonviable or dead. For all other patients cesarean section is the safest for both mother and baby. He believes that each patient must be individualized as so many factors such as parity, severity of the hemorrhage, viability of the fetus, etc., play a role. The general principle involved is to save the mother and if possible, to rescue the fetus.

RALPH A. REIS.

Nankivell, J. W.: Expulsion of a Placenta Praevia in Advance of the Foetus, *Brit. M. J.* 2: 527, 1937.

The case history is given of a multipara in whom two initial hemorrhages were followed several weeks later by the expulsion of the placenta two hours before the birth of the infant.

The literature contains only four references to similar expulsion of a placenta previa in advance of the fetus.

There was no extraordinary blood loss preceding or following expulsion in the case quoted.

F. L. ADAIR AND S. A. PEARL.

Lim, K. T.: A Comparative Study of 93 Cases of Placenta Praevia and 74 Cases of Abruptio Placentae, *Chinese M. J.* 53: 109, 1938.

The author reports 93 cases of placenta previa and 74 cases of abruptio placentae observed in 5,220 deliveries, during the last 14 years, in the Peiping Union Medical College.

Over 70 per cent of both types of cases were admitted to the hospital as emergency without any antenatal care, and a large number of them were critically ill and potentially infected.

Reduction of maternal and fetal mortalities depends on: The early hospitalization of these cases; not hastening delivery regardless of the general condition of the patient, and more liberal use of prophylactic transfusions.

C. O. MALAND.

Heim, K.: The Pathogenesis of Abruptio Placentae, *Monatschr. f. Geburtsh. u. Gynäk.* 104: 1, 1936.

The author found a definite relationship between hyperprolauria and pathologic conditions in pregnancy. Next to hydatid mole, the greatest output of prolan in the urine is to be found in cases of abruptio placentae, especially those cases designated as uteroplacental apoplexy. Likewise in eclampsia there is a great increase in prolan in the blood, in the cerebrospinal fluid and in the placenta. Hence, in the opinion of the author, abruptio placentae, pre-eclampsia, and eclampsia are dysharmonic toxemias of different symptomatology but of the same etiology.

If this conception is viewed in the light of quantitative disturbances in the physiologic function of the placenta, this theory is not different from other explanations.

In some cases of hyperemesis and toxemias during the early months of pregnancy, there are likewise very marked increases in the excretion of prolan. There is a possibility that the body can dispose of these excesses through the urine and cerebrospinal fluid. When, however, there is a retention of this excess in the tissues of the body, the disturbances which result are hydatid mole, abortion, or abruptio placentae. The cause of the premature separation of the placenta, especially of uteroplacental apoplexy, is a disturbance in the hormonal relationship between the placenta and the corpus luteum.

J. P. GREENHILL.

Batzfalvy, J.: Pathology and Surgical Treatment of Utero-Placental Apoplexy and Ablatio Placentae, Arch. f. Gynäk. 163: 552, 1937.

The author has collected the world statistics on ablatio placentae and uteroplacental apoplexy and presents his conclusions. The term "ablatio placentae" should be used for the milder cases of premature separation of the normally situated placenta and "uteroplacental apoplexy" for the severer forms of this condition. The frequency of uteroplacental apoplexy is difficult to determine since most authors have included the ablatio placentae figures in their reports. However, the frequency varies between 0.09 per cent and 1.06 per cent. There is no question that the uteroplacental apoplexy is a true pregnancy toxemia which can and frequently does result in fatal outcome to mother and child. It resembles other forms of toxemia and differs only in the location of the pathology which results. Such changes are found in the decidua, placenta, uterine wall, and uterine vessels.

The symptoms depend on this location and upon the extent of the resultant hemorrhage and the diagnosis and prognosis often depend on the extent of the placental separation, the latter also on the anatomic changes produced in the uterus, and the severity of the accompanying toxemia. The mortality ranges from 5, 10, 15, and 60 per cent.

Treatment should be obstetric for partial separation and "surgical" for complete separation. These latter methods and the results obtained are as follows: (1) vaginal cesarean section with a mortality of 45.4 per cent, (2) abdominal cesarean section, which should be the method of choice, with a mortality of 16.1 per cent, (3) precesarean hysterectomy, mortality 16.6 per cent, (4) uterine extirpation following cesarean section, mortality 35.3 per cent.

The results obtained can be definitely improved by early and accurate diagnosis followed by immediate appropriate treatment. If the uterine wall is normal and not involved the best treatment is conservative. Cesarean section should be done if there is hemorrhage into the uterine wall and the patient is in good condition. The uterus may be conserved only if this organ contracts readily, otherwise it must be removed. In the latter more severe type of case the risk is great but can be materially reduced by the use of frequent and early blood transfusions.

RALPH A. REIS.

Trillat, P., and Magnin, P.: Statistical and Critical Study of Retroplacental Hemorrhage Observed in 20,000 Labor Cases, Rev. franç. de gynéc. et d'obst. 33: 901, 1938.

In a series of 20,000 labor cases observed at the Lyon Midwives School, there were 66 instances of retroplacental hemorrhage. There were three forms, a mild type with survival of the infant (20 cases), a moderate type with fetal death but without serious consequences for the mother (42 cases) and a grave type, commonly known as the Couvelaire type with fetal death and serious prognosis for the mother (four cases).

Among the 66 cases were 34 instances without albuminuria. These cases were milder than those associated with the toxemias of pregnancy. This series of cases verified the belief that retroplacental hemorrhage is more serious and more frequent in multiparas and among women past 30 years of age. The total fetal mortality in this series was 70 per cent. There were only 2 maternal deaths and these occurred in the series of the four severe cases.

All of the patients were treated by artificial rupture of the membranes. The authors never resorted to surgical treatment.

J. P. GREENHILL.

Mahon, R.: Two Cases of Normal Labor After Preceding Severe Uterine Apoplexy, Bull. Soc. d'obst. et de gynéc. 27: 700, 1938.

The author reports two cases in which conservative cesarean section had been performed for grave uterine apoplexy and in which three and four years, respectively, after these operations, live children were born through the vagina. The author is not convinced that removal of the uterus improves the prognosis of uterine apoplexy. Among the 12 cases of severe uterine apoplexy observed and proved at laparotomy by Mahon the treatment was as follows: 5 conservative cesarean sections with 1 death, 5 cesarean sections followed by hysterectomy with 3 deaths, and 2 hysterectomies of unopened uteri with 1 death. The author favors conservative cesarean section because this operation saved 80 per cent of the mothers and retained their reproductive capacity, whereas hysterectomy saved only 50 per cent of the women and sacrificed their ability to have children. However, hysterectomy may have to be performed occasionally for intractable bleeding.

J. P. GREENHILL.

Currie, David: The Causes and Treatment of Retained Placenta, Brit. M. J. 2: 57, 1937.

Two types of retained placenta occur: one is simply a retained placenta, the other is adherent (placenta accreta or increta) which is very rare (1 in 6,000 to 1 in 4,000 births).

Retained placenta is characterized by a complete or partial separation of the placenta which is held in the upper segment of the uterus and gives rise to hemorrhage. The common cause of retention is atony or uterine inertia. Secondary causes may be a full urinary bladder or fibroids obstructing the passage.

In the presence of bleeding, manual removal must be prompt, though this is a method attended by a high morbidity and mortality.

A method for injecting the umbilical vein to effect separation and expulsion of the placenta is described. Sterile water may be used. In the Leeds Maternity Hospital, 186 cases had been injected; two ended fatally, and 8 were morbid. The incidence of manual removal dropped from 25 to 1 or 2 a year. The death rate in the former was 1.6 per cent as against 15.4 in the manual removal group, and the morbidity rate was 8 per cent as against 45.2 per cent. The method may be used in cases of post-partum hemorrhage and as a means of clearing the field before repair of episiotomy wounds or tears accompanying a difficult instrumental delivery.

F. L. ADAIR AND S. A. PEARL.

Tiemyeyer, A. C.: Placenta Accreta, South. M. J. 31: 608, 1938.

Two cases of placenta accreta are presented with a brief and concise analysis of the antecedents in the clinical history and the associated gross and microscopic pathologic changes. The incidence in the author's clinic was 1 in 4,312 deliveries.

As a result of an absence or a deficiency in the development of the decidua basalis, the placenta becomes organically attached to the uterine musculature,

thereby preventing the normal mechanism of separation of the placenta in the third stage of labor. There may be degrees of uteroplacental accretion from partial to complete, depending upon the area of the placental surface involved. Occasionally, placentas otherwise normally implanted may show mild evidences of the condition with attachment of a single cotyledon. Microscopically, the chorionic villi invade the musculature interdigitating with the fibers and bundles.

The first patient was 33 years of age and had 8 pregnancies in fourteen years, of which the seventh was complicated by prematurity, incomplete manual removal of a retained placenta necessitating subsequent curettage, hemorrhage, and puerperal sepsis with prolonged convalescence. She had the eighth spontaneous delivery in her home, and when the placenta failed to deliver two hours later, Cr   expression was ineffectually attempted followed by a manual removal of several pieces of placenta with associated bleeding. The uterus was packed. In the hospital the uterus was explored and efforts to remove the placenta were prevented by inability to find a line of cleavage. Bleeding and shock necessitated packing. Following two transfusions and recovery from shock, supravaginal hysterectomy was performed with successful outcome.

The second patient was a 20-year-old primigravida in whose history the only deviations from normal were a scantiness of menstruation and inability to become pregnant in three years. The present gestation terminated prematurely at thirty weeks. After a third stage of two hours followed by an unsuccessful Cr   maneuver and attempts at manual removal associated with hemorrhage the uterus was packed, a transfusion given, and supravaginal hysterectomy performed. Good recovery.

Placenta accreta is more common in multiparas than in primiparas. A history of previous manual removal of a placenta, sepsis, or curettement is significant. It has been suggested that disturbances of the corpus luteum may be an etiologic factor. Excessive erosive power of the trophoblastic villi, and insufficiency of antiferment production to check inordinate erosion have been suggested, but they do not explain the constant finding of a poorly developed decidua.

An important point in differential diagnosis between placenta accreta and placental incarceration as result of hourglass contraction of the uterus is found in the fact that in a case of placenta accreta there is no bleeding until attempts are made to remove it.

Manual attempts to separate the placenta and curettage are contraindicated. Shock and hemorrhage should be combated and supravaginal hysterectomy performed.

ARNOLD GOLDBERGER.

Irving, Frederick C., and Hertig, Arthur T.: A Study of Placenta Accreta, Surg. Gynec. Obst. 64: 178, 1937.

Eighteen clinical cases of placenta accreta are reported, and 86 others described in the literature are reviewed. The incidence in the clinic has been 1 case in every 1,956 deliveries.

The essential cause of this condition is partial or complete absence of the decidua basalis, so that the placenta is attached directly to the myometrium. In 12 of the cases the decidua vera was also examined and found to be normal in only 2 instances, thus indicating a generally defective development of the endometrium when the ovum was implanted.

Supravaginal hysterectomy with no attempt at manual extraction of the placenta yields excellent results, since of the 19 cases so treated, no mothers died. Attempt at manual extraction of the adherent placenta is extremely dangerous. Of the 30 cases in the combined series where this procedure was effected, 20 (66.6 per cent) died.

Transfusion should be employed in every case in which the blood loss exceeds, even by a small amount, the normal limit.

WILLIAM C. HENSKE.

King, Arthur G.: Placenta Accreta, Ohio State M. J. 34: 652, 1938.

Three cases of placenta accreta are presented bringing the total number of reported cases to 109. Two of these cases followed previous cesarean section and myomectomy with postoperative infection. The third was in a young para x whose last pregnancy terminated in an abortion. The treatment can be standardized on sound statistical evidence as: hysterectomy with no efforts at manual or instrumental removal of the placenta.

It is believed that placenta accreta is due to a mechanical, traumatic, or infectious insult to the endometrium combined with the chance that implantation will occur at the disturbed area. Endocrinopathy must be considered as a possible factor. Among the traumatic factors, serious consideration must be given to previous cesarean section, which was a likely etiologic factor in at least 6 per cent of all the reported cases. It is predicted that placenta accreta will become more common, particularly with the increased frequency of cesarean section.

The possibility of placenta accreta should be considered in any woman with a history of an endocrine disturbance, an abortion, or frequent pregnancies in rapid succession, and more particularly, a previous cesarean section. This possibility should militate against unnecessary abdominal deliveries, but might well bolster the argument for repetition of cesarean section.

J. P. GREENHILL.

Corinaldi, F.: Placental Abscess, Riv. ital. di ginec. 20: 180, 1937.

The author describes a case of placental abscess observed in a primipara, 25 years of age, after spontaneous birth of a seven months' live fetus. Both macroscopic and microscopic examinations revealed the abscess to have formed in the site of a thrombus. The cultures of the pus showed *Bacillus coli*. The author discusses the rarity and etiopathogenesis of this condition and demonstrates that the infection of the placenta was of hematogenous origin.

AUGUST F. DARO.

v. Pallos, K.: The Origin of Subchorial Cysts of the Placenta, Arch. f. Gynäk. 163: 63, 1936.

The author found gross subchorial cysts in 4.6 per cent of the 2,500 placentas examined. Following separation of chorion and amnion, the author was able to demonstrate subchorial cysts in 36.8 per cent with a hand lens. Microscopically, such cysts were demonstrable in every instance. The smallest cysts are by far the most common and are usually found in the outer third of the placenta. The large cysts are much less common and are found in the middle third of the placenta around the area where the larger placental vessels divide. These cysts arise most probably from basal ectoderm and are really trophoblastic. Degeneration of the cells of the trophoblast produces the cysts. Areas of necrosis are found surrounding the larger cysts; these are purely mechanical in origin and are due to pressure of the growing cysts on the cotyledons. These subchorial cysts are of interest embryologically and anatomically but have no clinical significance.

RALPH A. REIS.

Rhamy, B. W.: Chorioangiofibroma of the Placenta, J. Lab. & Clin. Med. 22: 899, 1937.

Chorioangiofibromas of the placenta are rare and presumably benign tumors. They vary in size from a grain of wheat to an apple, are sharply circumscribed and may be single or multiple. The author reports a case, the obstetric history of the patient being uneventful. The placenta was irregularly ovoid and contained 8 irregular, protruding, solid nodules which could be easily enucleated; they were covered by a fibrous capsule containing numerous blood vessels. Besides these eight protruding nodules, there were numerous smaller ones, varying

from 0.5 to 1.5 cm. in diameter, in the substance of the placenta. Microscopically, these tumors are separated from the placenta proper by a thick coat of compressed syncytium or Langhans's cells. The mass is composed of fibrous tissue containing capillaries of varying diameters lined with single layers of epithelium. The connective tissue is loosely areolar and consists of spider connective tissue cells. In the pinkish white areas, the connective tissue stroma is quite dense.

W. B. SERBIN

Marchetti, Andrew A.: A Consideration of Certain Types of Benign Tumors of the Placenta, Surg. Gynec. Obst. 68: 733, 1939.

Benign tumors of the placenta designated as chorioangiomas are relatively rare. On the basis of their histologic structure and pattern, these tumors are differentiated into several types: The cellular or immature, the vascular or more mature type, and that type accompanied by varying degrees of degenerative changes. These forms may intermingle in all gradations in the same tumor. The tissue originates from the chorionic mesenchyme, the proliferating endothelium and blood vessels playing the leading role, the stroma a subordinate or accessory role. Clinically chorioangiomas are of little significance.

WILLIAM C. HENSKEL

Item

American Board of Obstetrics and Gynecology

The written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, January 6, 1940, at 2:00 P.M. Formal notice of the place of examination will be sent each candidate several weeks in advance of the examination date. No candidate will be admitted to examination whose examination fee has not been paid at the Secretary's Office. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held in June, 1940.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II examinations must be on file in the Secretary's Office not later than March 15, 1940.

After January 1, 1942, there will be only one classification of candidates, and all will be required to take the Part I and Part II examinations.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

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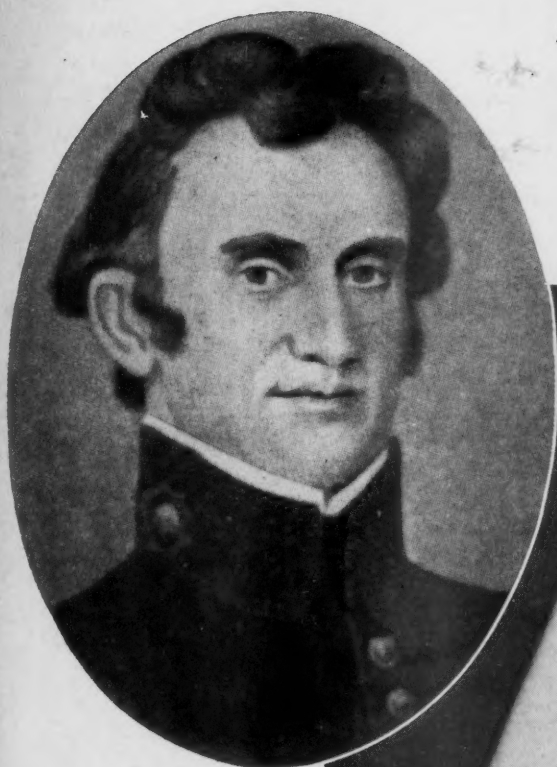
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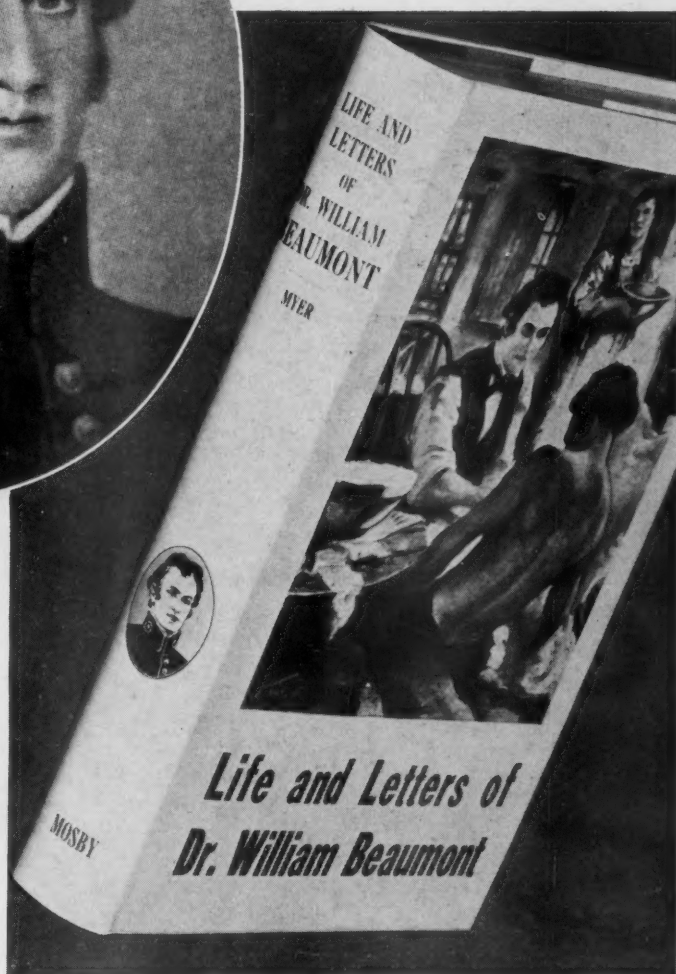
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